Exhibit 4

Exhibit 4

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XENOTRANSPLANTATION

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1. Clinical Study
Lessons from Clinical Islet Xenotransplantation in NZ

1

The evolution of successful islet xenotransplantation at Living Cell Technologies and Diatranz Otsuka Ltd

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In NZ in 1988 a 2 year old with Type 1 diabetes presented in hospital. His father asked if there was anything offered for treatment apart from daily blood tests and insulin injections. Early attempts at allotransplantation at that time had little or no success, and this was not available then or now. Xenotransplantation of encapsulated porcine islets as being reported by Sun et al in Toronto looked attractive. The child's father offered finances to start research in this direction and Diatranz was born; sufficient success in diabetic NOD mice using a microencapsulation technology devised by Calafiore et al provided incentive to expand activities. This culminated in two T1D patients receiving such intraperitoneal treatment in 1996 using neonatal pig islets and an encapsulation technique devised by Soon Shiong. Both showed a small clinical and biochemical response. One of these continued to show evidence of survival of the transplanted cells for over a decade.
Further development was halted by the potential threat posed by the discovery of human cell infectivity of pig endogenous retrovirus. The serendipitous discovery of a herd of pigs isolated from the rest of the world for nearly 200 years on a sub Antarctic island that were free of any detectable porcine viruses and with no detectable expression of DNA PERV provirus, allowed regulatory authorities in NZ after international and national public consultation to eventually approve a clinical safety trial in humans after relevant preclinical studies. Neonatal islets from these pigs were encapsulated in alginate/polyornithine and injected into the peritoneal cavity in escalating doses. The patients selected had all developed unaware hypoglycemia.
At smaller rather than larger doses, unaware hypoglycemia abated. Over 70 transplants have now been carried out with no evidence of zoonosis. Some dose related transient inflammatory side effects were noted after transplantation.
Improvements in islet isolation technology and encapsulation are expected to provide even better results in the future. Islet xenotransplantation carried out in this way is safe and has already provided a treatment at least as good as the best non-transplant alternatives.

2. Preclinical Studies in Pig-to-non-human Primate Model
Preclinical Efficacy

2-1

Questions regarding preclinical efficacy

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Several groups have reported pig islet (or embryonic pancreatic tissue) graft survival and function in nonhuman primates (NHPs) for periods of > 6 months, and on occasions for > 1 year. However, when 'free' (unencapsulated) islets are transplanted into the portal vein, there is a considerable early loss from the immediate blood-mediated inflammatory reaction (IBMIR), and rejection remains problematic. When encapsulated islets are transplanted, there remain problems with lack of nutrients reaching the islets and with rejection. There are also differences in glucose metabolism between pigs and NHPs that may affect the outcome.
Although considerable progress is being made, several questions continue to be asked, and some remain to be resolved:

1. What is the optimal site of transplantation?
2. Are neonatal or fetal islets preferred over adult islets?
3. Are islets from genetically-engineered pigs essential? In particular, will islets from pigs with deletion of both galactose and N-glycolylneuraminic acid be necessary before a successful clinical trial can be undertaken?
4. What is the optimum immunosuppressive regimen?
5. Are studies in the NHP model essential before a clinical trial can be undertaken? In particular, when encapsulated islets are to be transplanted without the need for exogenous immunosuppressive therapy, are trials in NHPs necessary?
6. Is it essential for the group planning the clinical trial to have experience of (i) pig islet isolation and/or (ii) management of immunosuppressed human islet allograft recipients?
7. Will it be necessary to house pigs under ideal isolation conditions or will it be sufficient to demonstrate that the islet 'product' that is to be transplanted is sterile?

In answer to these questions, the optimal site for transplantation remains uncertain, but most attention is being directed to the portal vein as this is the current approach for clinical islet allotransplantation. Neonatal pig islets might have some advantages over adult islets, and islets from genetically-engineered pigs certainly have advantages over those from wild-type pigs. There is not yet an agreed optimal immunosuppressive regimen, but those based on T cell depletion and costimulation blockade have shown considerable promise.
It is recommended that no clinical trial should be undertaken without some evidence in an animal model that there is the potential of benefit to the patient. However, studies in NHPs, although valuable, may not be essential if the clinical trial will involve encapsulated islets and the recipient will not receive exogenous immunosuppressive therapy, thus reducing the risks of the trial.
It is likely that national regulatory authorities will require the islet-source pigs to be housed under isolation conditions, and that groups initiating clinical trials have experience in pig islet isolation and, when 'free' islets are to be transplanted, in the management of immunosuppressed patients undergoing organ or, preferably, islet allotransplantation.

Preclinical Animal Model

2-2

Lessons from islet transplant studies in non-human primates

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Pig islet cell transplantation to the diabetic macaque is a broadly accepted and useful model to study safety and efficacy of xenograft products and/or immune interventions in the process of preclinical development. Diabetes reversal and long-term graft survival > 180 days has been achieved by several independent groups, however high inter-animal variability has been observed. Some common complications have been reported in long-term survivors, especially absence of body weight (BW) gain and even BW loss. Stress, toxicity, inflammation, malabsorption, and insufficient insulin are factors that contribute to complications. The standard small molecule immunosuppressants used in islet transplantation have a smaller efficacy-toxicity window in NHPs versus humans. Poor absorption of immunosuppression necessitates dose adjustments that result in chronic high gastrointestinal exposure to achieve acceptable systemic exposure in NHPs. GI injury resulting from toxicity can provoke lipid wasting, malabsorption, and inflammation.
In most studies efficacy has been associated with mild hyperglycemia in xenografted NHPs, which is attributed in part to metabolic differences between species.

Fasting glucose levels are lower in NHPs than in pigs or man, while C-peptide levels are higher and the insulin secretory capacity of porcine islets in vitro is similarly much lower than in man or monkeys. Likewise, energy metabolism as determined by caloric requirement is substantially higher in macaques than in humans or pigs. The pig-to-NHP model is much more stringent with regard to the amount and quality of porcine islets required than the pig-to- human setting, and effective dose will likely require adaptation.

Together, the effect on glycemic control and nutritional status in immunosuppressed macaques appears disproportionate to humans and may negatively bias safety data. Protein loss and hypoalbuminemia is strongly associated with poor clinical outcomes and consequently may increase infection/viral reactivation rates in preclinical studies.

NHPs are particularly stress sensitive and management of nonhuman primates in chronic survival studies is complicated, in particular under conditions of metabolic perturbations and chronic immunosuppression. We use refinement to reduce stress and enhance animal well-being, which reduces model-related confounding and improved interpretation when evaluating long-term survival studies.

The pig-to-nonhuman primate model of life-supporting islet transplantation shows limitations that are not apparent in short-term survival studies, but become manifest later after transplantation. These factors should be considered in the design and interpretation of pivotal preclinical studies in preparation for the phase transition to clinical trials.

3. Source Pigs, Islet Manufacturing and Releasing Testing

Mature Pig

3-1

Methods to maximize porcine islet yield

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Porcine islets are a potential source of cellular therapeutics for the treatment of type 1 diabetes. Porcine islet isolation, however, has proven surprisingly difficult due to the fragile nature of the islets themselves and wide yield variability depending on procedural technique and donor characteristics. The adult porcine pancreas is 2–3 times larger than a human pancreas but the available islet mass differs significantly by strain and age or even between individuals of the same litter. Therefore, our center has prioritized the discovery of donor screening methods and isolation techniques that ensure the greatest yield for the smallest investment. To facilitate appropriate donor selection, we have been investigating acute C-peptide response to intravenous glucose and to arginine stimulation, a test previously suggested to predict relative beta cell mass in human donors. In a very recent study, we also found that exposing weanling pigs to a high fat diet, enriched with soybean oil, boosted post-digestion islet mass. After a donor has been selected, the organ procurement technique can significantly improve porcine islet isolation outcomes. While flushing the entire pancreas is not feasible for large animals in a non-surgical environment, we have proven success by combining a selective arterial flush with ongoing surface cooling and ductal injection of cold preservation solution to remove blood content and reduce warm ischemic damage. We have proposed and implemented a dithizone (DTZ) scoring method in which a small tissue biopsy can be stained and rapidly assessed for islet quantity. We have correlated higher DTZ scores to greater islet isolation yields in multiple subsequent investigations. In addition to fast organ pre-screening, we have used tissue biopsy samples for more detailed immunohistochemical insulin staining to quantify functional islet density. This islet area fraction (IAF) scoring revealed that pancreata from young and adult porcine donors contain exocrine and endocrine tissue in a similar proportion to humans. Our findings suggest that it is possible to achieve a high porcine islet yield if optimal isolation methods can be identified and standardized. Digestion conditions, in particular, have been understudied. Since the non-availability of Liberase-PI, a variety of alternative collagenases and neutral proteases have become available. We have used collagen degradation assays and HPLC analysis to differentiate active ingredients in these compounds but while we continue to experiment with various enzyme combinations, an optimal blend to maximize porcine islet isolation yield has been determined. Finally, the greatest loss of islets often occurs during purification, wherein acinar-embedding and cell fragmentation can severely reduce yield. Efforts to improve post-purification recovery, in addition to the significant strides we have already made, will continue to improve the feasibility of an adequate porcine donor pool as islet xenotransplantation for clinical diabetic therapy draws closer to reality.

Neonatal Pig

3-2

Isolating and preparing neonatal porcine islet grafts for clinical transplantation

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Patients with brittle type 1 diabetes can now be protected from severe hypoglycemia and improved glycemic stability following islet transplantation. However, widespread application of this treatment will necessitate the need to develop an alternative to human donor islets. Studies have reported successful transplantation of porcine islets from fetal, neonatal, and adult porcine pancreases. In addition to studies in rodents, fetal porcine islets have been isolated from pigs of gestational age 60–69 days have been transplanted into patients with type 1 diabetes, whereas neonatal and adult porcine islets have been implanted into diabetic non-human primates. Therefore, xenotransplantation of porcine islets isolated from either fetal, neonatal, or adult animals have many strengths and are becoming closer to clinical application. This presentation will provide information on the technical aspects of isolating and preparing neonatal porcine islet grafts for clinical transplantation. Porcine islet product release criteria will also be presented that will be helpful in establishing the safety (endotoxin, sterility), identity/purity (cell composition), quantity (islet equivalents, cell number), vitality (membrane intactness), and potency (insulin secretory capacity) of biological porcine islet cell products.

4. Overcoming Immunological Hurdles by Immune Isolation

Microencapsulation

4-1

Microencapsulation

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The goals of our research are to develop safe and effective methods to promote the long-term functional survival of islet grafts in patients with Type 1 diabetes. We have focused our studies on donor islet immuno-isolation, using alginate microcapsules. Although the concept is not new, the availability of highly purified reagents and recently improved protocols for microcapsule generation have yielded promising results in both small animal models and in non-human primates. We have found that microencapsulation protects most murine islet allografts for > 1 year, without the need of host immunosuppression. This suggests that preventing cell contact between host immune cells and donor islets is sufficient to prevent allo-islet destruction. Similar results were found with encapsulated NOD islets in diabetic NOD recipients. Thus, encapsulation inhibits auto-immune damage to donor islets as well. We have extensive experience with a variety of encapsulated xeno-islets (porcine, rabbit, tilapia, non-human primate, human, rodent) transplanted in diabetic NOD and NOD Scid recipients. The biologic function of these encapsulated xeno-islets is remarkably normal in vivo. However, immuno-isolation alone is not sufficient to prevent the rejection of xeno-islets in our microcapsules. If recipients are treated with selective immuno-modulatory agents such as co-stimulatory blockade, most encapsulated porcine xeno-islet grafts function for > 1 year in NODs. Thus, immuno-suppression and donor islet immuno-isolation are synergistic in prolong the functional survival of islet xenografts in NODs. We have begun to test these concepts in diabetic non-human primates, and we have obtained only 1–2 months of partial graft function to date. Host immune cellular and cytokine responses have been limited, and our current microcapsules pre-

vent the entry of IgG. Thus, other mechanisms is donor islet injury must be involved; and these are the studies we are about to commence.

Monolayer Encapsulation

4-2

Islet Xenotransplantation: are we ready for clinical islet xenotransplantation? Use of a subcutaneous monolayer cellular device containing pig islets to treat diabetic primates without Immunosuppression.

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Although allogeneic islet transplantation can successfully cure type 1 diabetes, it has limited applicability: organs are in short supply; several human pancreas donors are often needed to treat one diabetic recipient; and immunosuppressive regimens, which are associated with side effects, are required to prolong survival of the islet graft. An alternative source of insulin-producing cells would therefore be of major interest. Pigs represent a possible source of alternative beta cells. Grafting of pig islets may appear difficult because of the immunologic species barrier, but pig islets have been shown to function in primates for at least 6 months with immunosuppression [1].

Therefore, a bioartificial pancreas, in which pig islets of Langerhans are encapsulated within a semipermeable membrane, may be an alternative therapeutic device for patients. It may constitute another safe and simple method of transplanting islets without the need for immunosuppressive therapy. Since the semipermeable membrane protects the islets from the host immune system, the islets are likely to survive and release insulin for a long period of time, thereby controlling glucose metabolism in the absence of immunosuppressive medication.

Recent data using macroencapsulation of pig islets in primates seems encouraging. In fact, a "monolayer" configuration of macroencapsulated pig islets (monolayer cellular device) implanted subcutaneously has been found to significantly improve diabetes control (glycated hemoglobin < 7%) in primates for 6 months without any immunosuppression [2]. In this encapsulation system, islets were seeded as a monolayer on an acellular collagen matrix, enhancing their interactions with a biologic membrane and increasing islet concentration per unit surface area. In addition, diabetes was controlled for up to 1 year in two diabetic primates after retransplantation with new monolayer cellular devices. Interestingly, diabetic control was completely maintained for > 32 weeks after the co-transplantation of adult pig islets and either bone marrow or adipose mesenchymal stem cells [3]. The co-transplantation of MSCs increased the vascularization of the monolayer device in terms of increase number of vessels and production of VEGF. By using this subcutaneous monolayer cellular device, a phase 1 clinical study is currently ongoing to assess the safety of this device for allotransplantation of encapsulated islets into humans. Up to now, one patient received such a subcutaneous implant containing human isolated islets which was well tolerated during 1 year and demonstrated a significant decrease of exogenous insulin needs.

In the field of micro/macroencapsulation, results now obtained without any immunosuppression may allow progression to pilot clinical trials as long as DPF pigs are used under GMP conditions.

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[3] Vériter S, Gianello P, Igarashi Y, Beaurin G, Ghyselinck A, Aouassar N, Jordan B, Gallez B, Dufrane D: Improvement of subcutaneous bioartificial pancreas vascularization and function by co-encapsulation of pig islets and mesenchymal stem cells in primates. Cell Transplant 2013, [Epub ahead of print].

Encapsulation for Clinical Application

4-3

Alginate PLO encapsulation for clinical application

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Xenotransplantation with porcine islets is a promising approach to overcome the shortage of human donors (1). Phase 1/2a xenotransplantation study of encapsulated neonatal porcine islets using alginate PLO capsules under the current New Zealand framework of regulations was conducted with promising results (2). In this study, we have optimized islet isolation and encapsulation processes for improving clinical outcomes.

Materials and Methods: Porcine pancreata were harvested from neonatal piglets. We optimized islet isolation method and capsulation method (optimized capsule) and compared with the current capsule (current capsule).

To assess in vitro function, static glucose stimulation tests were conducted with low glucose (L1: 50 mg/dL) followed by high glucose (H: 375 mg/dL) and low glucose again (L2: 50 mg/dL). Stimulation indices H/L1 and H/L2 were compared. To assess in vivo function, we transplanted marginal and sufficient numbers of encapsulated neonatal porcine islets into abdominal cavity of streptozotocin induced diabetic B6 mice. For negative control we infused saline into diabetic mice without islets. To ensure, the origin of insulin, we measured porcine C-peptide from the transplanted mice on day 32 post-transplant.

Results: Stimulation indices (H/L1) were 1.0 with the current capsule and 2.8 with the optimized capsule. Stimulation indices (H/L2) were 7.2 with the current capsule and 48.4 with the optimized capsule.

In vivo assay demonstrated that all three negative control mice died with high blood glucose on day 3, 3 and 15. When diabetic mice were transplanted with marginal number of islets, none of five mice reversed diabetes using the current capsules, but, two out of five mice could reverse diabetes using optimized capsules on day 3. When diabetic mice were transplanted with sufficient number of islets, four out of five mice reversed diabetes on day 3 but only two mice maintained normoglycemia at day 22 using the current capsules; however; three out of three mice using the optimized capsules could reverse diabetes on day 3 and all mice maintained normoglycemia at day 22.

With marginal number of transplantation, porcine C-peptide level was below detection levels with the current capsules and 0.15 ng/mL with the optimized capsules. With sufficient number of transplantation, the porcine C-peptide was 0.09 ng/mL with the current capsules and 0.35 ng/mL with the optimized capsules.

Conclusion: Optimized islet isolation and capsulation with alginate PLO could reliably reverse diabetes in mice with positive porcine C-peptide. This improved alginate PLO encapsulated neonatal islets might be able to improve clinical outcomes.

References: (1) Matsumoto S. Islet cell transplantation for type 1 diabetes. J Diabetes 2010; 2: 16–22.

(2) WHO. Second WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Geneva, Switzerland, 17–19 October 2011.

5. Overcoming Immunological Hurdles

Clinically Applicable Immunosuppressants and Tolerance

5-1

Clinically applicable immunosuppression and immunological tolerance

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Intraportal porcine islet xenotransplants have reversed diabetes for more than 6 months in nonhuman primates given anti-CD154 mAbs in combination with

other immunosuppressants (University of Minnesota: anti-IL-2R Abs + FTY720 + mTOR inhibitor ± leflunomide; Emory University/University of Alberta: anti-IL-2R Abs + belatacept + mTOR inhibitor; University of Pittsburgh: anti-thymocyte globulin + mycophenolate mofetil; Seoul National University: cobra venom factor + anti-ICAM mAb MD-3 or antithymocyte globulin or nTreg infusions + mTOR inhibitor). The thromboembolic risks associated with the administration of anti-CD154 mAbs preclude the clinical evaluation of these protocols. Of the several alternative immunotherapeutics tested in recent years as substitutes for anti-CD154 mAbs, only three have met with limited success. A regimen including belatacept used for maintenance in combination with a mTOR inhibitor and FTY720 prolonged islet xenograft survival for more than 6 months in two of two monkeys given anti-thymocyte globulin, anti-IL2R mAb, and rituximab for induction (Weizmann Institute). The anti-CD40 mAb Chi220 facilitated pig islet xenograft survival exceeding 6 months in one of six monkeys given in addition anti-IL2R mAb, belatacept, and mTOR inhibitor (Emory University/University of Alberta). Tacrolimus combined with anti-IL-2R mAb, abatacept, and mTor inhibitor prevented pig islet xenograft rejection in 21 of 25 monkeys; however increasing intestinal toxicity associated with this regimen in monkeys prevented their long-term follow-up in most study animals (University of Minnesota). More detailed immune mechanistic studies will be required to determine the precise immune recognition and effector pathways that were controlled by anti-CD154 immunotherapy in the above-referenced studies. Improved understanding of the immunobiology of islet xenotransplantation in nonhuman primates will facilitate the rational design of rejection prophylaxis protocols suitable for clinical investigation of islet xenotransplantation.

Preclinical research in the pig-to-nonhuman primate model is now also underway to explore the translatability of immunotherapeutic strategies that induced tolerance to pig islet grafts in immunocompetent rodents (e.g., immune-engineered pig islet grafts or peritransplant administration of donor antigen under the cover of transient B cell depletion and mTOR inhibition). Successful translation of these protocols and the induction of operational tolerance in the preclinical setting will likely require a multi-pronged approach that also includes genetic modification of the graft and/or targets the microenviroment of the implantation site to mitigate innate immune activation.

Genetic Modification of Source Pigs-1

5-2

Genetically engineered pigs as donors of pancreatic islets and as large animal models for testing the functionality of transplanted islets

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The transplantation of Langerhans islets to diabetic recipients might provide a long-lasting treatment for diabetes and has been implemented with considerable success, but the shortage of human organ donors restricts its future application to a very small proportion of potential recipients. For overcoming this limitation, the usage of Langerhans islets from a different source such as the pig pancreas represents an attractive alternative. Transplantation of encapsulated porcine pancreatic islets to type 1 diabetic patients with severe unaware hypoglycemia has already entered clinical studies. To overcome the rejection of pig islets by human T cells, we generated transgenic pigs expressing the optimized CTLA-4Ig variant LEA29Y in the pancreatic beta-cells. Neonatal islet cell clusters (ICCs) from INSLEA29Y transgenic (LEA-tg) pigs and wild-type controls were transplanted into streptozotocin-induced hyperglycemic NOD-scid IL2R-gamma null mice. Cloned LEA-tg pigs are healthy and exhibit a strong beta-cell specific transgene expression. LEA-tg ICCs displayed the same potential to normalize glucose homeostasis as wild-type ICCs after transplantation. After adoptive transfer of human peripheral blood mononuclear cells, transplanted LEA-tg ICCs were completely protected from rejection, whereas reoccurrence of hyperglycemia was observed in 80% of mice transplanted with wild-type ICCs. This study provided the first proof-of-principle report on transgenic pigs with beta-cell specific expression of LEA29Y and their successful application as donors in a xenotransplantation model. This approach may represent a major step toward the development of a novel strategy for pig-to-human islet transplantation without side effects of systemic immunosuppression (Klymiuk et al., Diabetes 2012; 61: 1527–1532).

To prevent apoptosis of beta-cells during isolation of Langerhans islets from the donor pancreas, in vitro cultivation, and the hypoxic stress phase in the early post-transplantation period, we generated transgenic pigs expressing the X-linked inhibitor of apoptosis (XIAP) under the control of the porcine INS promoter. So far, 10 INS-XIAP transgenic founders have been produced by somatic cell nuclear transfer using pools of stable transfected donor cells.

Engineered porcine islets which are less prone to undergo apoptosis as compared to wild-type pig islets should be interesting for micro- or macroencapsulation strategies. To establish a large animal model for testing such devices, we created the first pig model for permanent neonatal diabetes (PNDM) by expression of C94Y mutant insulin in the beta-cells of transgenic pigs (Renner et al., Diabetes 2013; 62: 1505–1511). This model develops a stable diabetic phenotype without further interventions such as streptozotocin treatment or pancreatectomy and should thus be ideally suited for testing the functionality of islet transplantation therapies.

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Genetic Modification of Source Pigs-2

5-3

Genetic modification of source pigs

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Intraportal pig islet xenografts face a range of immunological and process-related challenges, the most important of which are probably the instant blood-mediated inflammatory reaction (IBMIR) and T cell-mediated rejection (TCMR). Genetic modification of source pigs offers the opportunity to inhibit these destructive pathological mechanisms. Several approaches, including deletion of the xenoantigen alpha-Gal and/or transgenic expression of human complement regulators, have been shown to be protective in the pig to primate islet xenograft preclinical model. Transgenic secretion of the costimulation blockade molecule LEA29Y (belatacept) by donor islets has also been validated in a pig to humanized mouse model. We are developing a complementary strategy in which transgenic islet xenografts will secrete a chimeric anti-CD2 monoclonal antibody, to locally deplete infiltrating T cells and to block the costimulation of those that escape depletion. The antibody is suitable for both preclinical and clinical use because it recognises baboon and human T cells; it is unlikely to cause immunodeficiency in the transgenic pigs, which has been a problem for the pig CTLA4-Ig transgene, because it does not bind pig CD2.

One consideration when constructing islet-protective transgenes such as anti-CD2 is what promoter should be used to achieve optimal expression. Intuitively, islet-specific expression (e.g. using the insulin promoter) would seem to be the logical choice. However, as will be discussed, there are circumstances in which this may not be the case.

6. Clinical Trial Considerations Patient Selection and Informed Consent

6-1

Patient selection and informed consent for islet xenotransplantation

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Several clinical scenarios would justify trials of islet xenotransplantation, including islet after kidney (IAK) transplantation and islet xenotransplantation for hypoglycemia unawareness. In selecting a patient cohort, several factors unique to

xenotransplant trials must be considered, including the potential for xenozoonotic infective complications, the risks of immunosuppression and the requirement for lifelong monitoring. These factors need to be balanced against the benefits of improved glycemic control and ability to deliver large numbers of high-quality islets, something more difficult to achieve in islet allotransplantation. The importance of these risks varies depending on the patient cohort selected and proposed therapy to be undertaken. In islet xenotransplantation for hypoglycemia unawareness, immunosuppressive risks and problems with lifelong monitoring need special attention in trial design. Whereas in IAK xenotransplantation, consideration must be given to ensure that the procedure does not impact on renal allograft outcomes and patient co-morbidity, which is already significant in renal transplant recipients. With regards to informed consent islet xenotransplant trials are not different from other forms of clinical trials. Consent must be informed, voluntary and uncoerced. Depending on the trial, there may be potential risks to close contacts and what information they should receive would depend on what is proposed and the assessed risks. The major ethical issues relating to the consent process are the protocols for withdrawal from the trial and the requirement for lifelong or at least prolonged monitoring for infective complications. At present, no clear consensus exists as to the most appropriate patient group for the first trials of islet xenotransplantation. Rather, this will depend on the type of treatment being proposed, the potential infective risks and the overall burden of immunosuppression.

Infectious Disease Prevention

6-2

Infectious disease prevention and a response plan

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Transplantation of pig islet cells will almost certainly be the first type of xenotransplantation routinely performed in humans. Indeed, the first clinical trials have already been carried out.

As xenotransplantation using pig cells, tissues or organs may allow transmission of porcine microorganisms that are pathogenic for the recipient, donor pigs and transplant recipients should be carefully screened. Donor screening includes regular analysis of both the donor herd and the individual donor animal. Furthermore, the transplant, in the case of islet transplantation the islet cell preparation, should be subjected to analysis. Whereas most porcine microorganisms may be eliminated by qualified pathogen-free breeding, porcine endogenous retroviruses (PERVs) pose a special risk since they are part of the pig's genome. PERVs are released by normal pig cells and some can infect human cells. In particular, PERV-A and PERV-B are integrated into the genome of all pigs and can infect human cells. In contrast, PERV-C is not ubiquitous and only infects pig cells. However, recombinant PERV-A/C viruses have been described that also infect human cells and that are characterized by very high-titer replication. To prevent recombinations, pigs lacking PERV-C in their genome should be used for breeding multitransgenic pigs. Although blood cells can be used for analysis of PERV expression, differences in expression between organs have been described and should be taken into account. Fortunately, islet cells show only a low expression of PERV compared to other pig tissues.

Xenotransplant recipients should be tested for porcine microorganisms using direct and indirect methods. Direct methods include screening for the genetic information of the microorganisms using PCR, real-time PCR and real-time RT-PCR. In all of these, careful PCR contamination management is required to avoid false positive results. Indirect methods measure the immune response to infection. For example, antibody responses are analyzed using ELISA, Western blot assays and other related techniques. Indeed, such indirect methods are commonly used to detect infection with retroviruses such as HIV and HTLV. To exclude false positive results due to cross-reacting antibodies, the response to different proteins of the microorganisms should be analyzed. The recipients should also be screened for microorganisms that could infect and harm the porcine transplant.

In preparation for actual cases of transmission or infection of the transplant a response plan should be developed to deal with each potential microorganism.

Regulatory Framework

6-3

Regulatory framework for islet xenotransplantation in the USA, Europe and Germany

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In the Changsha Communiqué (2008), the World Health Organization (WHO) has summarized the regulatory requirements for xenotransplantation clinical trials. As stated in principle 4, clinical trials and procedures need to be effectively regulated because of the wider community risks of xenotransplantation. There should be no xenotransplantation in the absence of regulation by the government of the country. Regulation should have a legal basis to ban unregulated procedures and enforce compliance with regulatory requirements.

In the European Union (EU), clinical trials using xenogeneic medicinal products are effectively regulated. The European Directive 2005/28/EC and in particular its nationally transformed ordinances on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (GCP Ordinance) cover xenotransplantation. For the assessment by the ethics committee (German GCP Ordinance, Section 8) and for authorisation by the Competent Authority (CA; Section 9) it is declared that there shall be no time limit for assessment and authorization, respectively, in the case of trials of xenogeneic cell therapeutics. The German Medicinal Products Act (AMG) has transformed this definition for the procedures of the ethics committee and for authorisation by the national CA (Paul-Ehrlich-Institut) stating that no time limit with respect to the authorisation period shall apply in the testing of xenogeneic medicinal products (Section 42).

Both the GCP Ordinance and AMG regulate the need for submission of applications to the CA sending dossiers with documents concerning quality and manufacture, the pharmacological/toxicological tests, manufacturing permit, import permit, and documents concerning results of previous clinical trials and other clinical information which has come to light, as well as a summary of the risk/benefit assessment. In addition, evidence of insurance cover is required in the event that a person is killed or a person's body or health is injured during the course of the clinical trial. At least 500,000 € must be allocated for every case of death or permanent occupational disability of a person concerned by the clinical trial.

The European Medicines Agency (EMA) takes care of centralized regulatory procedures for medicinal products. The EMA Guideline on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009) deals with main criteria such as quality, non-clinical, clinical, pharmacovigilance and risk management plans, and particularly with requirements unique to xenogeneic specificities. The scientific and technical issues identified concern the sourcing and testing of animals, manufacture, quality control, as well as the non-clinical and clinical development of xenogeneic cell-based medicinal products. Relevant public health aspects are discussed and measures to ensure a proper surveillance for infections, including zoonoses are highlighted.

The Committee for Advanced Therapies (CAT) at the EMA is responsible for assessing the quality, safety and efficacy of Advanced Therapy Medicinal Products (ATMPs) and following scientific developments in the field. It is a multidisciplinary committee which was established in accordance with regulation 1394/2007/EC on ATMPs. In May 2013, EMA has published its scientific recommendation on classification of alginate encapsulated porcine pancreatic islet cells as ATMPs in accordance with 1394/2007/EC Article 17. The product is intended to be used for treating Type I diabetes, and might be considered to be effective in modifying abnormal glucose metabolism in Type I diabetics.

In the EU, compassionate use of medicinal products is a treatment option that allows the use of an unauthorised medicinal product to facilitate the availability to patients of new treatment options under development. Compassionate use programmes are often governed by legislation in individual EU Member States. In Germany, compassionate use is regulated by the Arzneimit*tel-Härtefall-Verordnung* (AMHV). In general, evidence and justification for a putatively safe and efficacious medicinal product is given by confirmatory (phase 3) clinical trials.

The German AMG has defined xenogeneic medicinal products that are intended for use in or on humans and which are or contain living animal tissues or cells (AMG, Section 4 subsection 21). Marketing authorizations are granted by the national CA, Paul-Ehrlich-Institut.

A manufacturing authorization is given by the local CA (AMG, Section 13) and if required, an import authorization is granted by the local CA (AMG, Section 72). Inspections of the corresponding manufacturing sites may be performed by the local CA prior to granting the import authorization.

In the USA, the Food and Drug Administration (FDA) has published considerations for allogeneic pancreatic islet cell products in September 2009. This guidance provides recommendations to manufacturers, sponsors, and clinical investigators involved in the clinical studies of allogeneic pancreatic islet cell products for the treatment of Type 1 diabetes mellitus. In April 2003, FDA has published guidance on the production, testing and evaluation of products intended for use in xenotransplantation (Guidance for Industry, Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans). One product is licensed in the USA.

Exhibit 5

Exhibit 5

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
AT427739T	PROTEIN-STABILISIERTE PHARMAZEUTISCHE WIRKSTOFFE UND DEREN VERWENDUNG	AT94442997	1997-09-24	US08720756	DESAI NEIL; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; ZHENG TIANLI; YAO ZHIWEN; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1996-10-01	2009-04-15
AU200230723B2	Novel Formulations of Pharmacological Agents, Methods for the Preparation Thereof and Methods for the Use Thereof.	AU2002300723	2002-08-19	AU8266298	Sahadevan, David C.; Magdassi, Shlomo; Soon-Shiong, Patrick; Desai, Neil P.	1998-06-26	2005-01-20
AU2002303626C1	Composition and methods for treatment of hyperplasia	AU2002303626	2002-05-02	US09847945	Desai, Neil P.; Soon-Shiong, Patrick	2001-05-02	2009-06-11
AU2003299590B8	Compositions and methods of delivery of pharmacological agents	AU2003299590	2003-12-09	US60526773; US60526544; US60527177; US60432317	Ci, Sherry Xiaopei; Desai, Neil P.; De, Tapas; Soon-Shiong, Patrick; Yang, Andrew; Trieu, Vuong; Beals Grim, Bridget; Yao, Qiang	2003-12-04; 2003-12-03; 2003-12	2010-04-08
AU2006202836B2	Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof	AU2006202836	2006-06-30	US09316642	Tao, Chunlin; Yao, Zhiwen; Magdassi, Shlomo; Louie, Leslie; Desai, Neil P; Soon-Shiong, Patrick; Yang, Andrew	1999-05-21	2009-10-08
AU2006213999B2	Combinations and modes of administration of therapeutic agents and combination therapy	AU2006213999	2006-02-21	US60654245	Soon-Shiong, Patrick; Desai, Neil P.	2005-02-18	2012-04-05
AU2006214100B2	Drugs with improved hydrophobicity for incorporation in medical devices	AU2006214100	2006-02-21	US60654175	Soon-Shiong, Patrick; Yu, Chengzhi; Wang, Qinwei; Tao, Chunlin; Desai, Neil P.	2005-02-18	2012-05-31
AU2006249235B2	Sparc and methods of use thereof	AU2006249235	2006-12-04	US60788208	Soon-Shiong, Patrick; Trieu, Vuong; Desai, Neil P	2006-03-31	2010-11-11
AU2006284657B2	Compositions and methods for preparation of poorly water soluble drugs with increased stability	AU2006284657	2006-08-30	WOUS06034103	Desai, Neil P.; Yim, Zachary; De, Tapas; Soon-Shiong, Patrick M. D.; Yang, Andrew	2006-08-30	2012-07-19
AU2006284808B2	Compositions comprising poorly water soluble pharmaceutical agents and antimicrobial agents	AU2006284808	2006-08-30	US60712865; US60736962; US60736931	Desai, Neil P.; Yang, Andrew; Soon-Shiong, Patrick M.D.; Selvaraj, Raj	2005-08-31; 2005-11-14; 2005-11	2012-08-16
AU2007317859B2	Nanoparticles of paclitaxel and albumin in combination with bevacizumab against cancer	AU2007317859	2007-11-06	US11594417	Soon-Shiong, Patrick; Desai, Neil P.	2006-11-06	2013-07-25
AU2007319763B2	SPARC and methods of use thereof	AU2007319763	2007-03-29	US60788208	Soon-Shiong, Patrick; Desai, Neil P.; Trieu, Vuong	2006-03-31	2011-11-24
AU2007333925B2	Triazine derivatives and their therapeutical applications	AU2007333925	2007-12-14	US60875057	Wang, Qinwei; Desai, Neil P.; Soon-Shiong, Patrick; Tao, Chunlin	2006-12-15	2013-10-31
AU2007334360B2	Breast cancer therapy based on hormone receptor status with nanoparticles comprising taxane	AU2007334360	2007-12-14	US60875004	Desai, Neil P.; Soon-Shiong, Patrick	2006-12-14	2013-10-17

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
AU200822333482	Nanoparticle comprising rapamycin and albumin as anticancer agent	AU2008223334	2008-03-07	US60905662; US60905663; US60905734; US60923456; US60905669; US60905735; US60905750; US60923248; US60905787; US60905767; US60905672	Desai, Neil P.; Trieu, Vuong; Soon-Shiong, Patrick	2007-03-07; 2007-03-07; 2007-03	2014-05-08
AU2008260447B2	Methods and compositions for treating recurrent cancer	AU2008260447	2008-06-02	US60932750	Desai, Neil P.; Soon-Shiong, Patrick	2007-06-01	2013-10-10
AU2010236382B2	Prion-free nanoparticle compositions and methods	AU2010236382	2010-04-15	US61169665; US61238052	Desai, Neil P.; Peykov, Viktor; Soon-Shiong, Patrick	2009-04-15; 2009-08-28	2016-01-14
AU2010286670B2	Combination therapy with nanoparticle compositions of taxane and hedgehog inhibitors	AU2010286670	2010-08-25	US61236813	Tao, Chunlin; Desai, Neil P.; Soon-Shiong, Patrick	2009-08-25	2016-04-21
AU2011232862B2	Methods of enhancing drug delivery and effectiveness of therapeutic agents	AU2011232862	2011-03-28	US61318777	Desai, Neil P.; Soon-Shiong, Patrick	2010-03-29	2016-03-03
AU2011261684B2	Methods of treating bladder cancer	AU2011261684	2011-05-20	US61396800; US61449513	Desai, Neil P.; Soon-Shiong, Patrick	2010-06-02; 2011-03-04	2016-09-15
AU2011261685B2	Methods of treatment of pancreatic cancer	AU2011261685	2011-05-20	US61377035; US61446932; US61351846	Desai, Neil P.; Soon-Shiong, Patrick	2010-08-25; 2011-02-25; 2010-06	2016-02-11
AU2012201568B2	Combinations and modes of administration of therapeutic agents and combination therapy	AU2012201568	2012-03-16	AU2012201568	Soon-Shiong, Patrick; Desai, Neil	2012-03-16	2014-07-31
AU2012202903B2	Drugs with improved hydrophobicity for incorporation in medical devices	AU2012202903	2012-05-17	AU2012202903	Desai, Neil P.; Soon-Shiong, Patrick; Tao, Chunlin; Yu, ChengZhi; Wang, Qinwei	2012-05-17	2014-12-11
AU2012207030B2	Compositions Comprising Poorly Water Soluble Pharmaceutical Agents And Antimicrobial Agents	AU2012207030	2012-07-26	AU2012207030	Desai, Neil P.; Selvaraj, Raj; Yang, Andrew; Soon-Shiong, Patrick M.D.	2012-07-26	2014-12-18
AU2013204187B2	NANOPARTICLE COMPRISING RAPAMYCIN AND ALBUMIN AS ANTICANCER AGENT	AU2013204187	2013-04-12	AU2013204187	DESAI, Neil P.; SOON-SHIONG, Patrick; TRIEU, Vuong	2013-04-12	2015-10-01
AU2013204198B2	Combinations and modes of administration of therapeutic agents and combination therapy	AU2013204198	2013-04-12	AU2013204198	DESAI, Neil P.; SOON-SHIONG, Patrick	2013-04-12	2016-04-21
AU2014200528B2	TRIAZINE DERIVATIVES AND THEIR THERAPEUTICAL APPLICATIONS	AU2014200528	2014-01-30	AU2014200528	Tao, Chunlin; Wang, Qinwei; Desai, Neil P.; Soon-Shiong, Patrick	2014-01-30	2016-05-12
AU718753B2	Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof	AU4592997	1997-09-24	US08720756	NEIL P DESAI; CHUNLIN TAO; ANDREW YANG; LESLIE LOUIE; TIANLI ZHENG; ZHIWEN YAO; PATRICK SOON-SHIONG; SHLOMO MAGDASSI	1996-10-01	2000-04-20
AU784416B2	Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof	AU5035900	2000-05-19	US09316642	NEIL P DESAI; CHUNLIN TAO; ANDREW YANG; LESLIE LOUIE; ZHIWEN YAO; PATRICK SOON-SHIONG; SHLOMO MAGDASSI	1999-05-21	2006-03-30

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
BRPI9711856B1	métodos para preparação de um agente ativo, substancialmente insolúvel em água e composição para liberação in vivo de um agente ativo	BRPI9711856	1997-09-24	US08720756	YANG ANDREW; TAO CHUNLIN; LOUIE LESLIE; DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; ZHENG TIANLI; YAO ZHIWEN	1996-10-01	2016-07-12
BRPI9715297B1	composição compreendendo partículas de agente farmacologicamente ativo, uso da mesma, cateter intravenoso, frasco selado e emulsão compreendendo um agente farmacologicamente ativo	BRPI9715297	1997-09-24	US08720756; BRPI9711856	YANG ANDREW; TAO CHUNLIN; LOUIE LESLIE; DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; ZHENG TIANLI; YAO ZHIWEN	1996-10-01; 1997-09-24	2016-07-12
CA2263765C	METHODS FOR THE PRODUCTION OF PROTEIN PARTICLES USEFUL FOR DELIVERY OF PHARMACOLOGICAL AGENTS	CA2263765	1997-08-19	US60023968	MAGDASSI, SHLOMO; DESAI, NEIL; FERRERI, KEVIN; SOON-SHIONG, PATRICK	1996-08-19	2010-03-30
CA2267498C	PROTEIN STABILIZED PHARMACOLOGICALLY ACTIVE AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF	CA2267498	1997-09-24	US08720756	DESAI, NEIL P.; TAO, CHUNLIN; YANG, ANDREW; LOUIE, LESLIE; ZHENG, TIANLI; YAO, ZHIWEN; SOON-SHIONG, PATRICK; MAGDASSI, SHLOMO	1996-10-01	2007-05-08
CA2294981C	NOVEL FORMULATIONS OF PHARMACOLOGICAL AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF	CA2294981	1998-06-26	US60051021; US08926155	DESAI, NEIL P.; SOON-SHIONG, PATRICK; MAGDASSI, SHLOMO; SAHADEVAN, DAVID C.	1997-06-27; 1997-09-09	2012-04-03
CA2371912C	PROTEIN STABILIZED PHARMACOLOGICALLY ACTIVE AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF	CA2371912	2000-05-19	US09316642	DESAI, NEIL P.; TAO, CHUNLIN; YANG, ANDREW; LOUIE, LESLIE; YAO, ZHIWEN; SOON-SHIONG, PATRICK; MAGDASSI, SHLOMO	1999-05-21	2010-02-16
CA2446083C	COMPOSITION AND METHODS FOR TREATMENT OF HYPERPLASIA	CA2446083	2002-05-02	US09847945	DESAI, NEIL P.; SOON-SHIONG, PATRICK	2001-05-02	2015-01-06
CA2509365C	COMPOSITIONS AND METHODS OF DELIVERY OF PHARMACOLOGICAL AGENTS	CA2509365	2003-12-09	US60432317; US60526544; US60526773; US60527177	DESAI, NEIL P.; YANG, ANDREW; CI, SHERRY XIAOPEI; DE, TAPAS; TRIEU, VUONG; SOON-SHIONG, PATRICK; BEALS GRIM, BRIDGET; YAO, QIANG	2002-12-09; 2003-12-03; 2003-1	2012-08-07
CA2512487C	PROTEIN STABILIZED PHARMACOLOGICALLY ACTIVE AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF	CA2512487	1997-09-24	US08720756	DESAI, NEIL P.; TAO, CHUNLIN; YANG, ANDREW; LOUIE, LESLIE; ZHENG, TIANLI; YAO, ZHIWEN; SOON-SHIONG, PATRICK; MAGDASSI, SHLOMO	1996-10-01	2012-05-29

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
CA2598213C	DRUGS WITH IMPROVED HYDROPHOBICITY FOR INCORPORATION IN MEDICAL DEVICES	CA2598213	2006-02-21	US60654175	DESAI, NEIL P.; TAO, CHUNLIN; YU, CHENGZHI; WANG, QINWEI; SOON-SHIONG, PATRICK	2005-02-18	2011-04-19
CA2598510C	Q3 SPARC DELETION MUTANT AND USES THEREOF	CA2598510	2006-02-17	US60654261	TRIEU, VUONG; DESAI, NEIL P.; SOON-SHIONG, PATRICK	2005-02-18	2011-12-20
CA2620389C	COMPOSITIONS AND METHODS FOR PREPARATION OF POORLY WATER SOLUBLE DRUGS WITH INCREASED STABILITY	CA2620389	2006-08-30	WOUS06034103	DE, TAPAS; DESAI, NEIL P.; YANG, ANDREW; YIM, ZACHARY; SOON-SHIONG, PATRICK M. D.	2006-08-30	2014-06-17
CA2620585C	COMPOSITIONS COMPRISING POORLY WATER SOLUBLE PHARMACEUTICAL AGENTS AND ANTIMICROBIAL AGENTS	CA2620585	2006-08-30	US60712865; US60736962; US60736931	DESAI, NEIL P.; SELVARAJ, RAJ; YANG, ANDREW; SOON-SHIONG, PATRICK M.D.	2005-08-31; 2005-11-14; 2005-1	2015-04-28
CA2648118C	METHODS USING SPARC FOR PREDICTING THE RESPONSE OF A TUMOUR TO CHEMOTHERAPY AGENTS	CA2648118	2007-03-29	US60788208	TRIEU, VUONG; DESAI, NEIL P.; SOON-SHIONG, PATRICK	2006-03-31	2013-01-08
CA2672893C	TRIAZINE DERIVATIVES AND THEIR THERAPEUTICAL APPLICATIONS	CA2672893	2007-12-14	US60875057	DESAI, NEIL P.; SOON-SHIONG, PATRICK; TAO, CHUNLIN; WANG, QINWEI	2006-12-15	2016-02-23
CA2689914C	USE OF PROTEIN-BOUND TAXANE NANOPARTICLES IN THE TREATMENT OF RECURRENT GYNECOLOGICAL CANCERS	CA2689914	2008-06-02	US60932750	DESAI, NEIL P.; SOON-SHIONG, PATRICK	2007-06-01	2016-08-16
CN100525748C	药剂的新制剂及其制备和应用方法	CN200310121217	1998-06-26	US08926155; US60051021	内尔·P·代塞; 帕奇克·苏一雄; 什落莫·马格达西; 大卫·C·沙哈地万; 内尔·P·代塞; 帕奇克·苏一雄; 什落莫·马格达西; 大卫·C·沙哈地万	1997-09-09; 1997-06-27	2009-08-12
CN100588396C	治疗增生的组合物和方法	CN02811017	2002-05-02	US09847945	N·P·德赛; P·孙雄	2001-05-02	2010-02-10
CN101160123B	治疗剂的组合	CN200680011677	2006-02-21	US60654245	N·P·德塞; P·颂雄	2005-02-18	2013-07-17
CN101291658B	用于制备稳定性增加的水难溶性药物的组合物和方法	CN200680038640	2006-08-30	US60712865; US60736962; US60736931	T·德; N·P·德赛; A·杨; Z·因; P·M·D·顺-希昂	2005-08-31; 2005-11-14; 2005-1	2014-04-16
CN101454673B	SPARC及其使用方法	CN200780019544	2007-03-29	US60788208	V·特里鲁; N·P·德塞; P·索恩-希翁	2006-03-31	2014-02-12
CN102460167B	不含朊病毒的纳米颗粒组合物和方法	CN201080026604	2010-04-15	US61169665; US61238052	N·P·德塞; V·裴科夫; P·孙雄	2009-04-15; 2009-08-28	2015-07-22
CN102573832B	利用紫杉烷和刺猬抑制剂的纳米颗粒组合物的联合治疗	CN201080045983	2010-08-25	US61236813	C·陶; N·P·德赛; P·孙雄	2009-08-25	2015-07-22

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
CN1515244B	蛋白质稳定的药理活性物质及其它的制备和应用方法	CN200310123461	1997-09-24	US08720756	内尔·P·代塞; 陶春林; 安杰·杨; 莱斯烈·路易; 郑天立; 姚志文; 帕奇克·苏·雄; 什落莫·马格达西	1996-10-01	2013-08-07
CN1980699B	利用白蛋白-结合蛋白作为靶标的治疗方法	CN200580020748	2005-05-16	US60571622; US60654261	V·特利乌; N·P·德赛; P·苏恩·施昂	2004-05-14; 2005-02-18	2012-03-21
CY1112907T1	ΣΥΝΔΥΑΣΜΟΙ ΚΑΙ ΤΡΟΠΟΙ ΧΟΡΗΓΗΣΗΣ ΘΕΡΑΠΕΥΤΙΚΩΝ ΠΑΡΑΓΟΝΤΩΝ ΚΑΙ ΘΕΡΑΠΕΙΑ ΣΥΝΔΥΑΣΜΟΥ	CY121100013	2012-01-05	EP06735710	DESAI Neil P; SOON-SHIONG Patrick; DESAI Neil P; SOON-SHIONG Patrick	2006-02-21	2016-04-13
DE69739348D1	PROTEIN-STABILISIERTE PHARMAZEUTISCHE WIRKSTOFFE UND DEREN VERWENDUNG	DE69739348	1997-09-24	US08720756	DESAI NEIL P; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; ZHENG TIANLI; YAO ZHIWEN; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1996-10-01	2009-05-20
DK1023050T3	NYE FORMULERINGER AF FARMAKOLOGISKE MIDLER, FREMGANGSMÅDER TIL FREMSTILLINGEN DERAF OG FREMGANGSMÅDER TIL ANVENDELSEN DERAF	DK98932874	1998-06-26	US08926155	SAHADEVAN DAVID C; DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1997-09-09	2013-10-14
DK2097078T3	NANOPARTIKLER AF PACLITAXEL OG ALBUMIN I KOMBINATION MED BEVACIZUMAB MOD KRÆFT	DK07839976	2007-11-06	US11594417	DESAI NEIL P; SOON-SHIONG PATRICK	2006-11-06	2014-05-12
DK2470173T3	Kombinationsterapi med nanopartikelsammensætninger af taxan og hedgehog-inhibitorer	DK10812593	2010-08-25	DK10812593	TAO CHUNLIN; DESAI NEIL P; SOON-SHIONG PATRICK	2010-08-25	2016-06-06
DK2481405T3	Nanopartikler af paclitaxel og albumin i kombination med bevacizumab mod kræft	DK12154995	2007-11-06	US11594417	DESAI NEIL P; SOON-SHIONG PATRICK	2006-11-06	2016-06-06
DK2552415T3	Fremgangsmåder til behandling af cancer	DK11763292	2011-03-28	DK11763292	SOON-SHIONG PATRICK; DESAI NEIL P	2011-03-28	2016-11-28
DK961612T3	Protein-stabiliserede-farmakologisk-aktive-midler og deres anvendelse	DK97944429	1997-09-24	US08720756	DESAI NEIL P; ZHENG TIANLI; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; YAO ZHIWEN	1996-10-01	2009-06-15
DK961612T4	Protein-stabiliserede, farmakologisk aktive midler og deres anvendelse	DK97944429	1997-09-24	US08720756	TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; YAO ZHIWEN; DESAI NEIL P; ZHENG TIANLI; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1996-10-01	2012-10-08
EP1023050B1	ZUSAMMENSETZUNGEN VON PHARMAKOLOGISCHEN WIRKSTOFFEN, VERFAHREN ZU DEREN HERSTELLUNG UND DEREN VERWENDUNG	EP98932874	1998-06-26	US08051021; US08926155	DESAI, Neil, P.; SOON-SHIONG, Patrick; MAGDASSI, Shlomo; SAHADEVAN, David, C.	1997-06-27; 1997-09-09	2013-09-25
EP1755653B1	BEHANDLUNGSMETHODEN UNTER VERWENDUNG VON ALBUMINBINDENDEN PROTEINEN ALS TARGETS	EP05804826	2005-05-16	US60571622; US60654261	TRIEU, Vuong; DESAI, Neil P.; SOON-SHIONG Patrick	2004-05-14; 2005-02-18	2014-12-31
EP1853250B1	KOMBINATIONEN UND MODI ZUR VERABREICHUNG THERAPEUTISCHER MITTEL UND KOMBINATIONSTHERAPIE	EP06735710	2006-02-21	WOUS06006167; US60654245	DESAI, Neil, P.; SOON-SHIONG, Patrick	2006-02-21; 2005-02-18	2011-11-02

Publication Number	Title	Application Number	Application/Filing Date	Priority Number(s)	Inventor	Priority Date(s)	Publication Date
EP1944019B1	Verfahren zur Herstellung proteinstabilisierter pharmakologisch aktiver Wirkstoffe	EP08006374	1997-09-24	US720756	Desai, Neil, P.; Tao, Chunlin; Yang, Andrew; Louie, Leslie; Zheng, Tianli; Yao, Zhiwen; Soon-Shiong, Patrick; Magdassi, Shlomo	1996-10-01	2016-09-07
EP2091919B1	DERIVATE VON 18-AMINO-SUBSTITUIERTEN ANALOGA DES GELDAMYCIN-HYDROCHINONS MIT CYCTOTOXISCHER WIRKUNG FÜR DIE BEHANDLUNG VON KREBS	EP07854639	2007-11-14	WOUS07084662; US60865977	TAO, Chunlin; HAN, Hongna; SUN, Xiaowen; DESAI, Neil; SOON-SHIONG, Patrick	2007-11-14; 2006-11-15	2011-08-17
EP2097078B1	NANOTEILCHEN VON PACLITAXEL UND ALBUMIN IN KOMBINATION MIT BEVACIZUMAB GEGEN KREBS	EP07839976	2007-11-06	US11594417	DESAI, Neil P.; SOON-SHIONG, Patrick	2006-11-06	2014-04-16
EP2155188B1	VERFAHREN UND ZUSAMMENSETZUNGEN ZUR BEHANDLUNG EINES TUMORREZIDIVS	EP08768111	2008-06-02	US60932750	DESAI, Neil, P.; SOON-SHIONG, Patrick	2007-06-01	2013-10-09
EP2425840B1	Triazinderivate und deren therapeutische Anwendungen	EP11007839	2007-12-14	US60875057	Desai, Neil P.; Soon-Shiong, Patrick; Tao, Chunlin; Wang, Qinwei	2006-12-15	2015-04-08
EP2470173B1	KOMBINATIONSTHERAPIE MIT NANOPARTIKELZUSAMMENSETZUNGEN AUS TAXAN UND HEDGEHOG-HEMMERN	EP10812593	2010-08-25	US61236813	TAO, Chunlin; DESAI, Neil, P.; SOON-SHIONG, Patrick	2009-08-25	2016-04-27
EP2481405B1	Nanoteilchen von Paclitaxel und Albumin in Kombination mit Bevacizumab gegen Krebs	EP12154995	2007-11-06	US594417	Desai, Neil P.; Soon-Shiong, Patrick	2006-11-06	2016-03-23
EP2552415B1	VERFAHREN ZUR BEHANDLUNG VON KARZINOMEN	EP11763292	2011-03-28	US61318774; US61433132	DESAI, Neil, P.; SOON-SHIONG, Patrick	2010-03-29; 2011-01-14	2016-09-07
EP961612B2	PROTEIN-STABILISIERTE PHARMAZEUTISCHE WIRKSTOFFE UND DEREN VERWENDUNG	EP97944429	1997-09-24	US08720756	DESAI, Neil, P.; TAO, Chunlin; YANG, Andrew; LOUIE, Leslie; ZHENG, Tianli; YAO, Zhiwen; SOON-SHIONG, Patrick; MAGDASSI, Shlomo	1996-10-01	2012-08-01
ES2323559T5	Agentes farmacológicamente activos revestidos con proteína y su utilización	ES97944429	1997-09-24	US08720756	DESAI NEIL P; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; ZHENG TIANLI; YAO ZHIWEN; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1996-10-01	2012-12-03
ES2435944T3	Nuevas formulaciones de agentes farmacológicos, métodos para su preparación y métodos para su uso	ES98932874	1998-06-26	US08926155	DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; SAHADEVAN DAVID C	1997-09-09	2013-12-26
ES2469716T3	Nanopartículas de paclitaxel y albúmina en combinación con bevacizumab contra el cáncer	ES07839976	2007-11-06	US11594417	DESAI NEIL P; SOON-SHIONG PATRICK	2006-11-06	2014-06-18
ES2576289T3	Nanopartículas de paclitaxel y albúmina en combinación con bevacizumab contra el cáncer	ES12154995	2007-11-06	US11594417	DESAI NEIL P; SOON-SHIONG PATRICK	2006-11-06	2016-07-06
ES2577024T3	Terapia combinada con composiciones de nanopartículas de taxano e inhibidores de Hedgehog	ES10812593	2010-08-25	ES10812593	TAO CHUNLIN; DESAI NEIL P; SOON-SHIONG PATRICK	2010-08-25	2016-07-12

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HK1024866A1	PROTEIN STABILIZED PHARMACOLOGICALLY ACTIVE AGENTS AND THEIR USE	HK00103153	2000-05-27	US08720756	LOUIE LESLIE; DESAI NEIL P; SOON-SHIONG PATRICK; TAO CHUNLIN; ZHENG TIANTLI; YANG ANDREW; MAGDASSI SHLOMO; YAO ZHIWEN	1996-10-01	2009-11-13
HK1030543A1	NOVEL FORMULATIONS OF PHARMACOLOGICAL AGENTS, METHODS FOR THE PREPARATION THEREOF AND METHODS FOR THE USE THEREOF	HK01100752	2001-02-02	US08926155	DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; DAVID C SAHADEVAN	1997-09-09	2014-04-17
HK1109589A1	COMBINATIONS AND MODES OF ADMINISTRATION OF THERAPEUTIC AGENTS AND COMBINATION THERAPY	HK08104204	2008-04-14	WOUS06006167; US60654245	DESAI NEIL P; SOON-SHIONG PATRICK	2006-02-21; 2005-02-18	2012-01-06
HK1119071A1	COMBINATIONS OF THERAPEUTIC AGENTS	HK08111140	2008-10-08	HK08111140	DESAI NEIL P; SOON-SHIONG PATRICK	2008-10-08	2014-04-04
HK1140944A1	METHODS AND COMPOSITIONS FOR TREATING RECURRENT CANCER	HK10107362	2010-08-03	HK10107362	DESAI NEIL P; SOON-SHIONG PATRICK	2010-08-03	2014-06-27
HK1210045A1	用包含紫杉烷的納米顆粒基於激素受體狀態治療乳腺癌	HK15110929	2015-11-05	HK15110929	·德塞; ·孫雄; ·德塞; ·孫雄	2015-11-05	2016-04-15
HRP20131142T1	POSTUPCI I PRIPRAVCI ZA LIJEÄŠENJE RECIDIVA RAKA	HRP20131142	2013-11-28	HRP20131142	Desai, Neil P.; Soon-Shiong, Patrick; Desai, Neil P.; Soon-Shiong, Patrick	2013-11-28	2014-01-03
HRP20160551T8	KOMBINIRANA TERAPIJA S PRIPRAVCIMA NANOČESTICA TAKSANA I HEDGEHOG INHIBITORA	HRP20160551	2016-05-23	EP10812593	Tao, Chunlin; Desai, Neil P.; Soon-Shiong, Patrick; Tao, Chunlin; Desai, Neil P.; Soon-Shiong, Patrick	2010-08-25	2016-11-18
HU230338B1	Novel formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof	HU0003972	1998-06-26	US08926155	DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; SAHADEVAN DAVID C	1997-09-09	2016-02-29
MX337149B	NUEVAS FORMULACIONES DE AGENTES FARMACOLOGICOS, METODOS PARA SU PREPARACION Y METODOS PARA EL USO DE LOS MISMOS.	MX12014591	1998-06-26	US08926155	DESAI NEIL P; SOON-SHIONG PATRICK; MAGDASSI SHLOMO; SAHADEVAN DAVID C	1997-09-09	2016-02-15
MX339142B	COMBINACIONES Y METODOS DE ADMINISTRACION DE AGENTES TERAPEUTICOS Y TERAPIA DE COMBINACION.	MX2011009748	2006-02-21	MX2011009748	DESAI NEIL P; SOON-SHIONG PATRICK	2006-02-21	2016-05-13
NO328689B1	Proteinstabiliserte farmakologisk virksomme midler, fremgangsmate for fremstilling av disse og fremgangsmate for anvendelse av disse.	NO991620	1999-04-06	US08720756	SOON-SHIONG PATRICK; DESAI NEIL P; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; ZHENG TIANLI; YAO ZHIWEN; MAGDASSI SHLOMO	1996-10-01	2010-04-26
NO332166B1	Formuleringer av paklitaksel	NO996433	1999-12-23	US08926155	SOON-SHIONG PATRICK; DESAI NEIL P; MAGDASSI SHLOMO; SAHADEVAN DAVID C	1997-09-09	2012-07-09
PT1023050E	NOVAS FORMULAÇÕES DE AGENTES FARMACOLÓGICOS, MÉTODOS PARA A SUA PREPARAÇÃO E MÉTODOS PARA A SUA UTILIZAÇÃO	PT09893287	1998-06-26	US08926155	MAGDASSI SHLOMO; SOON-SHIONG PATRICK; DESAI NEIL P; SAHADEVAN DAVID C	1997-09-09	2013-12-04
PT2097078E	NANOPARTÍCULAS DE PACLITAXEL E ALBUMINA EM COMBINAÇÃO COM BEVACIZUMAB CONTRA O CANCRO	PT07839976	2007-11-06	US11594417	SOON-SHIONG PATRICK; DESAI NEIL P	2006-11-06	2014-07-25

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PT2470173E	TERAPIA DE COMBINAÇÃO COM COMPOSIÇÕES NANOPARTICULADAS DE TAXANO E INIBIDORES HEDGEHOG	PT10812593	2010-08-25	PT10812593	PATRICK SOON-SHIONG; NEIL P DESAI; CHUNLIN TAO	2010-08-25	2016-06-15
PT2481405E	NANOPARTÍCULAS DE PACLITAXEL E ALBUMINA EM COMBINAÇÃO COM BEVACIZUMAB CONTRA O CANCRO	PT12154995	2007-11-06	US11594417	PATRICK SOON-SHIONG; NEIL P DESAI	2006-11-06	2016-06-08
PT961612E	AGENTES FARMACOLOGICAMENTE ACTIVOS ESTABILIZADOS POR PROTEÍNA E SUA UTILIZAÇÃO	PT97944429	1997-09-24	US08720756	MAGDASSI SHLOMO; SOON-SHIONG PATRICK; DESAI NEIL P; TAO CHUNLIN; YANG ANDREW; ZHENG TIANLI; LOUIE LESLIE; YAO ZHIWEN	1996-10-01	2009-06-17
SI2097078T1	Nanodelci paklitaksela in albumina v kombinaciji z bevacizumabom proti raku	SI200731475	2007-11-06	US11594417; EP07839976	DESAI Neil P.; SOON-SHIONG Patrick; DESAI Neil P.; SOON-SHIONG Patrick	2006-11-06; 2007-11-06	2014-07-31
SI2481405T1	Nanodelci paklitaksela in albumina v kombinaciji z bevacizumabom proti raku	SI200731795	2007-11-06	US11594417; EP12154995	Desai Neil P.; Soon-Shiong Patrick; Desai Neil P.; Soon-Shiong Patrick	2006-11-06; 2007-11-06	2016-08-31
UA101610C2	НАНОЧАСТИЦА, КОТОРАЯ СОДЕРЖИТ РАПАМИЦИН И АЛЬБУМИН, В КАЧЕСТВЕ ПРОТИВОРАКОВОГО АГЕНТА	UA2009010156	2008-03-07	UA2009010156	Дисей Нейл П.; Соон-Шыонг Патрик; Триеу Вуонг; Дисей Нейл П.; Соон-Шыонг Патрик; Триеу Вуонг	2008-03-07	2013-04-25
UA110196C2	COMBINATION THERAPY COMPOSITION OF NANOPARTICLES OF TUCSON AND INHIBITORS HEDZHHOH	UA201203446	2010-08-25	UA201203446	TAO CHUNLIN; DESAI NEIL P; SOON-SHIONG PATRICK	2010-08-25	2015-12-10
UA96273C2	КОМПОЗИЦИЯ ДОЦЕТАКСЕЛА И ЦИТРАТА ДЛЯ ЛЕЧЕНИЯ РАКА	UA2008003886	2006-08-30	UA2008003886	Де Тапас; Дисей Нейл П.; Янг Эндрю; Им Захари; Соон-Шионг Патрик М. Д.; Де Тапас; Дисей Нейл П.; Янг Эндрю; Им Захари; Соон-Шионг Патрик М. Д.	2006-08-30	2011-10-25
US5916596A	Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof	US08720756	1996-10-01	US08720756	DESAI NEIL P; TAO CHUNLIN; YANG ANDREW; LOUIE LESLIE; ZHENG TIANLI; YAO ZHIWEN; SOON-SHIONG PATRICK; MAGDASSI SHLOMO	1996-10-01	1999-06-29
US5997904A	Total nutrient admixtures as stable multicomponent liquids or dry powders and methods for the preparation thereof	US08723805	1996-09-30	US08412726; US08023698	MAGDASSI SHLOMO; YANG ANDREW; TAO CHUNLIN; DESAI NEIL P; YAO ZHIWEN; SOON-SHIONG PATRICK	1995-03-29; 1993-02-22	1999-12-07
US6096331A	Methods and compositions useful for administration of chemotherapeutic agents	US08926155	1997-09-09	US08720756; US08485448; US08200235; US08023698; US08035150	DESAI NEIL P; SOON-SHIONG PATRICK	1996-10-01; 1995-06-07; 1994-0	2000-08-01

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US6506405B1	Methods and formulations of cremophor-free taxanes	US09628388	2000-08-01	US09628388; US08926155; US08720756; US08485448; US08200235; US08035150; US08023698	Desai, Neil P.; Soon-Shiong, Patrick	2000-08-01; 1997-09-09; 1996-1(	2003-01-14
US6528067B1	Total nutrient admixtures as stable multicomponent liquids or dry powders and methods for the preparation thereof	US09457085	1999-12-07	US09457085; US08412726; US08023698; US08723805	Magdassi, Shlomo; Yang, Andrew; Tao, Chunlin; Desai, Neil P.; Yao, Zhiwen; Soon-Shiong, Patrick	1999-12-07; 1995-03-29; 1993-0	2003-03-04
US6537579B1	Compositions and methods for administration of pharmacologically active compounds	US09574763	2000-05-19	US09574763	Desai, Neil P.; Soon-Shiong, Patrick	2000-05-19	2003-03-25
US6749868B1	Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof	US09316642	1999-05-21	US09316642	Desai, Neil P.; Tao, Chunlin; Yang, Andrew; Louie, Leslie; Yao, Zhiwen; Soon-Shiong, Patrick; Magdassi, Shlomo	1999-05-21	2004-06-15
US6753006B1	Paclitaxel-containing formulations	US09629501	2000-07-31	US09629501; US08926155; US08720756; US08485448; US08200235; US08023698	Desai, Neil P.; Soon-Shiong, Patrick	2000-07-31; 1997-09-09; 1996-1(	2004-06-22
US7332568B2	Q3 SPARC deletion mutant and uses thereof	US11356829	2006-02-17	US60654261	Trieu, Vuong ; Desai, Neil P. ; Soon-Shiong, Patrick	2005-02-18	2008-02-19
US7700612B2	Di-ester prodrugs of camptothecin, process for their preparation and their therapeutical applications	US10583803	2004-12-23	US11583803	Soon-Shiong, Patrick ; Desai, Neil P. ; Tao, Chunlin ; Yu, Cheng Zhi	2004-12-23	2010-04-20
US7758891B2	Combinations and modes of administration of therapeutic agents and combination therapy	US12334115	2008-12-12	US12334115	Desai, Neil P. ; Soon-Shiong, Patrick	2008-12-12	2010-07-20
US7771751B2	Compositions comprising poorly water soluble pharmaceutical agents and antimicrobial agents	US11514030	2006-08-30	US11514030	Desai, Neil P. ; Selvaraj, Raj ; Yang, Andrew ; Soon-Shiong, Patrick	2006-08-30	2010-08-10
US7780984B2	Methods and compositions for treating proliferative diseases	US11880314	2007-07-20	US11880314	Desai, Neil P. ; Soon-Shiong, Patrick ; De, Tapas K.	2007-07-20	2010-08-24
US7799954B2	Dicarbonyl derivatives and methods of use	US11939909	2007-11-14	US11939909	Tao, Chunlin ; Wang, Qinwei ; Trieu, Vuong ; Desai, Neil ; Soon-Shiong, Patrick	2007-11-14	2010-09-21
US7816346B2	Analogs of ansamycin and pharmaceutical compositions thereof	US11940644	2007-11-15	US11940644	Tao, Chunlin ; Han, Hongna ; Sun, Xiaowen ; Desai, Neil ; Soon-Shiong, Patrick	2007-11-15	2010-10-19
US7820788B2	Compositions and methods of delivery of pharmacological agents	US11553339	2006-10-26	US11553339	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2006-10-26	2010-10-26
US7858782B2	Triazine derivatives and their therapeutical applications	US11956883	2007-12-14	US11956883	Tao, Chunlin ; Wang, Qinwei ; Desai, Neil P. ; Soon-Shiong, Patrick	2007-12-14	2010-12-28

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US7923536B2	Compositions and methods of delivery of pharmacological agents	US12758413	2010-04-12	US12758413	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2010-04-12	2011-04-12
US7981445B2	Compositions and methods for preparation of poorly water soluble drugs with increased stability	US12402358	2009-03-11	WOUS06034103	De, Tapas ; Desai, Neil P. ; Yang, Andrew ; Yim, Zachary ; Soon-Shiong, Patrick	2006-08-30	2011-07-19
US8026275B2	Compositions, methods of use and preparation of 2,6-diisopropyl phenol and analogs for ischemic injury	US11816311	2006-02-17	US11816311	Desai, Neil P. ; Tao, Chunlin ; Yu, Cheng Zhi ; Trieu, Vuong ; Soon-Shiong, Patrick	2006-02-17	2011-09-27
US8034375B2	Combinations and modes of administration of therapeutic agents and combination therapy	US11359286	2006-02-21	US11359286	Desai, Neil P. ; Soon-Shiong, Patrick	2006-02-21	2011-10-11
US8034765B2	Compositions and methods for preparation of poorly water soluble drugs with increased stability	US11513756	2006-08-30	US11513756	De, Tapas ; Desai, Neil P. ; Yang, Andrew ; Yim, Zachary ; Soon-Shiong, Patrick	2006-08-30	2011-10-11
US8137684B2	Formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof	US11520523	2006-09-12	US11520523	Desai, Neil P. ; Tao, Chunlin ; Yang, Andrew ; Louie, Leslie ; Soon-Shiong, Patrick	2006-09-12	2012-03-20
US8138229B2	Compositions and methods of delivery of pharmacological agents	US12910693	2010-10-22	US12910693	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2010-10-22	2012-03-20
US8257733B2	Methods and compositions for treating proliferative diseases	US11544242	2006-10-06	US11544242	Desai, Neil P. ; Soon-Shiong, Patrick ; De, Tapas	2006-10-06	2012-09-04
US8268348B2	Combinations and modes of administration of therapeutic agents and combination therapy	US13228323	2011-09-08	US13228323	Desai, Neil P. ; Soon-Shiong, Patrick	2011-09-08	2012-09-18
US8314156B2	Compositions and methods of delivery of pharmacological agents	US13038287	2011-03-01	US13038287	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2011-03-01	2012-11-20
US8415304B2	Sparc and methods of use thereof	US12295068	2007-03-29	US12295068	Trieu, Vuong ; Desai, Neil P. ; Soon-Shiong, Patrick	2007-03-29	2013-04-09
US8420603B2	SPARC and methods of use thereof	US11599100	2006-11-14	US11599100	Trieu, Vuong ; Desai, Neil P. ; Soon-Shiong, Patrick	2006-11-14	2013-04-16
US8580786B2	Triazine derivatives and their therapeutical applications	US12971786	2010-12-17	US12971786	Desai, Neil P. ; Soon-Shiong, Patrick ; Tao, Chunlin ; Wang, Qinwei	2010-12-17	2013-11-12
US8735394B2	Combinations and modes of administration of therapeutic agents and combination therapy	US12436697	2009-05-06	US12436697	Desai, Neil P. ; Soon-Shiong, Patrick	2009-05-06	2014-05-27
US8846771B2	Compositions and methods of delivery of pharmacological agents	US13649987	2012-10-11	US13649987	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2012-10-11	2014-09-30
US8853260B2	Formulations of pharmacological agents, methods for the preparation thereof and methods for the use thereof	US11520479	2006-09-12	US11520479	Desai, Neil P. ; Soon-Shiong, Patrick	2006-09-12	2014-10-07
US8911786B2	Nanoparticle comprising rapamycin and albumin as anticancer agent	US12530188	2008-03-07	US12530188	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2008-03-07	2014-12-16
US8916204B2	SPARC and methods of use thereof	US13800132	2013-03-13	US13800132	Trieu, Vuong ; Desai, Neil P. ; Soon-Shiong, Patrick	2013-03-13	2014-12-23
US8927019B2	Methods and compositions for treating recurrent cancer	US12600991	2008-06-02	US12600991	Desai, Neil P. ; Soon-Shiong, Patrick	2008-06-02	2015-01-06

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US8946169B2	SPARC and methods of use thereof	US13791009	2013-03-08	US13791009	Trieu, Vuong ; Desai, Neil P. ; Soon-Shiong, Patrick	2013-03-08	2015-02-03
US8999396B2	Breast cancer therapy based on hormone receptor status with nanoparticles comprising taxane	US13779624	2013-02-27	US13779624	Desai, Neil P. ; Soon-Shiong, Patrick	2013-02-27	2015-04-07
US9012518B2	Compositions and methods of delivery of pharmacological agents	US13777980	2013-02-26	US13777980	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2013-02-26	2015-04-21
US9012519B2	Compositions and methods of delivery of pharmacological agents	US13777988	2013-02-26	US13777988	Desai, Neil P. ; Soon-Shiong, Patrick ; Trieu, Vuong	2013-02-26	2015-04-21
US910154 3B2	Combinations and modes of administration of therapeutic agents and combination therapy	US13585696	2012-08-14	US13585696	Desai, Neil P. ; Soon-Shiong, Patrick	2012-08-14	2015-08-11
US9308180B2	Compositions and methods for preparation of poorly water soluble drugs with increased stability	US13408994	2012-02-29	US13408994	De, Tapas ; Desai, Neil P ; Yang, Andrew ; Yim, Zachary ; Soon-Shiong, Patrick	2012-02-29	2016-04-12
US9393318B2	Methods of treating cancer	US13073824	2011-03-28	US13073824	Desai, Neil P. ; Soon-Shiong, Patrick	2011-03-28	2016-07-19
US9399071B2	Methods of treatment of pancreatic cancer	US13701002	2011-05-20	US13701002	Desai, Neil P. ; Soon-Shiong, Patrick	2011-05-20	2016-07-26
US9399072B2	Methods of treatment of pancreatic cancer	US13783122	2013-03-01	US13783122	Desai, Neil P. ; Soon-Shiong, Patrick	2013-03-01	2016-07-26
US9446003B2	Prion free nanoparticle compositions and methods of making thereof	US14191279	2014-02-26	US14191279	Desai, Neil P. ; Peykov, Viktor ; Soon-Shiong, Patrick	2014-02-26	2016-09-20

Exhibit 6

Exhibit 6

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Phase I and Pharmacokinetic Study of ABI-007, a Cremophor-free, Protein-stabilized, Nanoparticle Formulation of Paclitaxel[1]

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ABSTRACT

Purpose: **ABI-007 is a novel Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. The absence of Cremophor EL may permit ABI-007 to be administered without the premedications used routinely for the prevention of hypersensitivity reactions. Furthermore, this novel formulation permits a higher paclitaxel concentration in solution and, thus, a decreased infusion volume and time. This Phase I study examines the toxicity profile, maximum tolerated dose (MTD), and pharmacokinetics of ABI-007.**

Experimental Design: **ABI-007 was administered in the outpatient setting, as a 30-min infusion without premedications. Doses of ABI-007 ranged from 135 (level 0) to 375 mg/m^2 (level 3). Sixteen patients participated in pharmacokinetic studies.**

Results: **Nineteen patients were treated. No acute hypersensitivity reactions were observed during the infusion period. Hematological toxicity was mild and not cumulative. Dose-limiting toxicity, which occurred in 3 of 6 patients treated at level 3 (375 mg/m^2), consisted of sensory neuropathy (3 patients), stomatitis (2 patients), and superficial keratopathy (2 patients). The MTD was thus determined to be 300 mg/m^2 (level 2). Pharmacokinetic analyses revealed paclitaxel C_{max} and area under the curve$_{inf}$ values to increase linearly over the ABI-007 dose range of 135–300 mg/m^2. C_{max} and area under the curve$_{inf}$ values for individual patients correlated well with toxicity.**

Conclusions: **ABI-007 offers several features of clinical interest, including rapid infusion rate, absence of requirement for premedication, and a high paclitaxel MTD. Our results provide support for Phase II trials to determine the antitumor activity of this drug.**

INTRODUCTION

Paclitaxel is a chemotherapeutic agent with a wide spectrum of antitumor activity when used as monotherapy or in combination chemotherapy regimens (1). The drug is used extensively in the treatment of advanced carcinomas of the breast, ovary, head and neck, and lung. Research into its activity in prostate cancer and urothelial tumors is ongoing as well. On the basis of early reports suggesting a dose-response phenomenon (2, 3), and in keeping with standard medical oncology practice, attempts are generally made to maintain paclitaxel doses at or near the MTD.[3] Several schedules of administration have been studied, each demonstrating a slightly different toxicity profile. Short infusions of 1–3 h result in peripheral neuropathy as a dose-limiting toxicity, whereas longer, continuous infusion schedules produce a higher incidence of neutropenia (2, 4–6). Other common side effects include alopecia, mucositis, arthralgias, myalgias, and mild nausea.

The paclitaxel preparation in clinical use (Taxol; Bristol-Myers Squibb, Princeton, NJ) is formulated in the nonionic surfactant Cremophor EL (polyoxyethylated castor oil) and ethanol to enhance drug solubility (7). Cremophor EL may add to paclitaxel's toxic effects by producing or contributing to the well-described hypersensitivity reactions that commonly occur during infusion, affecting 25–30% of treated patients (8, 9). To minimize the incidence and severity of these reactions, premedication with histamine 1 and 2 blockers, as well as glucocorticoids (usually dexamethasone), has become standard practice (10). The cumulative side effects of dexamethasone used as a premedication may add to treatment-related morbidity and, in some instances, result in early discontinuation of therapy. Cremaphor EL may also contribute to chronic paclitaxel toxic effects, such as peripheral neuropathy (11). An additional problem arising from the Cremophor and ethanol solvent is the leaching of plasticizers from PVC bags and infusion sets in routine clinical use (12). Consequently, Taxol must be prepared and administered in either glass bottles or non-PVC infusion systems and with in-line filtration. These problematic issues have spurred interest in the development of taxanes with improved solubility in aqueous solutions (13).

ABI-007 is a novel Cremophor-free formulation of paclitaxel (14). It is prepared by high-pressure homogenization of paclitaxel in the presence of human serum albumin, resulting in a nanoparticle colloidal suspension. Like Taxol, ABI-007 dos-

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[3] The abbreviations used are: MTD, maximum tolerated dose; ANC, absolute neutrophil count; AUC, area under the curve; CL, clearance; PVC, polyvinyl chloride.

Table 1 Dose levels

Level	Dose (mg/m^2)	No. patients entered	No. cycles
0	135	4	6
1	200	3	38
2	300	6	35
3	375	6	17

age is determined by the paclitaxel content of the formulation, making direct comparison of the two drugs possible. ABI-007 can be reconstituted in normal saline at concentrations of 2–10 mg/ml, compared with 0.3–1.2 mg/ml for Taxol. Thus, the volume and time required for administration is reduced. In the absence of Cremophor EL, the risk of hypersensitivity reactions should decrease significantly, and patients receiving ABI-007 might thus avoid premedication. Moreover, there is no danger of leaching plasticizers from infusion bags or tubing, and conventional PVC infusion systems may be safely used.

To explore the potential clinical utility of ABI-007, we have conducted a Phase I study of this drug for patients with advanced solid tumors. The objectives of this trial were to determine the toxic effects, MTD, and pharmacokinetic profile of this unique paclitaxel preparation.

PATIENTS AND METHODS

Patient Eligibility and Evaluation on Study. Eligible patients included those with a diagnosis of an advanced solid tumor, having failed standard therapy. Requirements included a Zubrod performance status of 0–3, an expected survival of >6 weeks, hemoglobin $\geq$ 9 g/dl, ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, serum creatinine $<$ 2 mg/dl, and serum bilirubin $<$ 1.5 mg/dl. Patients with prior exposure to taxanes were eligible for the study.

Pretreatment evaluations included a complete blood count with differential and platelet count, serum chemistry profile, chest radiograph, and electrocardiogram. Baseline imaging studies and serum tumor marker levels were obtained at the discretion of the treating physician. Brain imaging by computerized tomography or magnetic resonance imaging was required for patients with symptoms suggestive of central nervous system involvement. Evaluations performed during the study included a complete blood count with differential and platelet count at least once weekly and a chemistry profile prior to each course. Restaging was performed after every 2nd or 3rd cycle of therapy. Patients were removed from the study for progression of disease, unacceptable toxicity, or at the patient's request.

Study Design. This Phase I study was conducted at The University of Texas M. D. Anderson Cancer Center and was approved by the M. D. Anderson Institutional Review Board. Informed consent was obtained from all subjects. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose levels of ABI-007 are shown in Table 1. Dose escalation followed the standard "3 + 3" rule. Briefly, 3 patients were accrued at the starting dose level. If no toxic effects greater than grade 2 were observed, 3 patients were entered at the next dose level. If, at any level, one of the first 3 patients experienced a grade 3 or 4 toxic effect, 3 additional patients were entered at that dose level. The MTD was defined as one dose level below that at which $\geq$2 patients experienced grade 3 or 4 toxic effects. Six patients were to be treated at the MTD. Patients were permitted to escalate to the next higher dose level if no significant toxic effects were observed after the first 2 cycles of therapy. Patients with toxicity greater than grade 2 were permitted to reduce dosage by one dose level and remain on therapy at the discretion of the treating physician.

Treatment. ABI-007 was supplied by American Bioscience, Inc. (Santa Monica, CA). All therapy was administered in the outpatient treatment center of the M. D. Anderson Cancer Center, with the exception of patients participating in pharmacokinetic studies, which required an overnight hospital stay. The prescribed dose of ABI-007 was prepared in 100–150 ml of 0.9% saline. The drug was administered i.v. without in-line filtration and without premedication. For the first 3 patients on study, the total dose of ABI-007 was administered at a rate of 1.4 mg/kg/h or roughly over 3 h. If no acute hypersensitivity reactions were noted, the remainder of the patients were to receive treatment over 30 min. One cycle of therapy was 21 days.

Pharmacokinetic Studies. Pharmacokinetic studies were performed in 16 patients, with at least 3 patients representing each dose level. Whole blood samples of 5 ml each were taken to determine the pharmacokinetics of ABI-007 at 13 time points: 0, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, and 48 h. Paclitaxel was extracted from whole blood samples using protein precipitation with acetonitrile, followed by solid phase extraction. The sample extracts were analyzed for paclitaxel using liquid chromatography atmospheric pressure ionization tandem mass spectrometry. The limit of quantitation for paclitaxel is 5 ng/ml, and the range of reliable response is 5–1000 ng/ml.

Pharmacokinetic parameters were determined from each patient's whole blood/plasma paclitaxel concentration profile. Analysis was performed by the noncompartmental routine using WinNonlin software (Pharsight Corp., Mountain View, CA). The peak or maximum paclitaxel concentration (C_{max}) and the corresponding peak time (t_{max}) were observed values. The elimination constant ($\lambda 12_z$) was obtained by log-linear regression analysis of the terminal phase of the whole blood/plasma concentration *versus* time profile. The elimination half-life ($T_{1/2}$) was determined by taking the ratio of natural log of 2 and $\lambda 12_z$. The AUC from time 0 to time infinity (AUC_{inf}) was obtained by summation of AUC_{last} (AUC from time 0 to last measurable concentration, calculated by the linear trapezoidal rule) and AUC_{ext} (extrapolated area, estimated by taking the ratio between the last measurable concentration and $\lambda 12_z$). The dose area relationship (*i.e.*, total ABI-007 dose divided by AUC_{inf}) was used to determine total body CL. The volume of distribution (V_z) was determined by taking the ratio between CL and $\lambda 12_z$.

Descriptive statistics (mean, median, SD, coefficient of variation, maximum, and minimum) were computed for pertinent pharmacokinetic parameters by ABI-007 dose. Regression analysis of mean AUC_{inf} *versus* dose was performed to gain an appreciation of pharmacokinetic linearity, if evident, for the dose range evaluated in this trial. Differences in the means of C_{max} and AUC_{inf} between groups of patients were analyzed for significance using a two-tailed, two-sample *t* test. Pearson's

Table 2 Patient characteristics

	No. (%)
Enrolled	20
Eligible	19
Age (yr)	
Median	50
Range	33–83
Performance status (Zubrod)	
0	2 (10)
1	14 (74)
2	3 (16)
Gender	
Female	16 (84)
Male	3 (16)
Malignancy	
Breast cancer	13 (68)
Melanoma	6 (32)
Prior treatment	
Chemotherapy	19 (100)
Immunotherapy	6 (32)
Radiotherapy	15 (79)

correlation coefficient was used to examine the correlation between degree of myelosuppression and C_{max} or AUC_{inf}.

RESULTS

Patients. Twenty patients were enrolled in the trial. One of these chose not to be treated after signing an informed consent. Therefore, 19 patients received drug and were evaluable for toxic effects. Patient characteristics are summarized in Table 2.

Treatment and MTD Determination. All treatment was administered without dexamethasone or histamine 1 or 2 blockers. The first 3 patients received infusions of ABI-007 over 2–3 h. No hypersensitivity reactions were observed. Therefore, all subsequent infusions were administered over 30 min. Even at the faster infusion rate, there were no instances of acute hypersensitivity to the ABI-007 preparation.

Three patients were entered initially at level 0, receiving 135 mg/m^2 over 3 h. One of these experienced progression of disease over the next several weeks, with rapid clinical deterioration, making it difficult to ascertain toxic effects of ABI-007 in this individual. To verify toxicity data at this dose level and ascertain the safety of administering the drug over a short infusion period, a 4th patient was entered at level 0 and was the first patient to receive drugs over 30 min. There were no instances of grade 3 or 4 toxicity observed at dose levels 0 or 1 (200 mg/m^2). At dose level 2 (300 mg/m^2), 1 of the first 3 patients developed grade 3 sensory neuropathy. Three more patients were accrued at this level, with no additional observations of dose-limiting toxicity. At dose level 3 (375 mg/m^2), during the 1st cycle of treatment, one of the first 3 patients experienced grade 3 sensory neuropathy, grade 3 stomatitis, and a visual disturbance diagnosed as superficial keratopathy, also grade 3. An additional 3 patients were accrued at level 3. One patient from this second cohort experienced a similar spectrum of grade 3 toxic effects, including sensory neuropathy, stomatitis, and superficial keratopathy; this patient developed grade 3 vomiting and diarrhea and thrombocytopenia as well. An additional case of sensory neuropathy, this time as an isolated grade 3 toxic effect, was observed in a 3rd patient at level 3. The study was thus terminated. The MTD for ABI-007 administered as a 30-min infusion every 21 days, as determined by this study, was 300 mg/m^2. The dose-limiting toxic effects were sensory neuropathy, stomatitis, and superficial keratopathy. Specific toxic effects are described below.

Table 3 Median absolute neutrophil and platelet nadirs by dose level

Dose level	ANC nadir × 10^3/mm^3 (range)	Platelet nadir × 10^3/mm^3 (range)
0	2.229 (1.850–5.040)	204 (174–292)
1	1.845 (0.586–3.729)	197 (118–270)
2	0.960 (0.264–3.680)	200 (105–609)
3	0.966 (0.018–1.804)	173 (25–251)

Hematological Toxicity. Hematological toxicity was dose dependent but remained modest throughout the study (Table 3). Of the 96 treatment cycles administered, only 7 (7.3%) resulted in an ANC nadir < 500/mm^3, 6 of which occurred above the MTD at dose level 3. There was one hospital admission for febrile neutropenia. In only one case did the platelet count drop below 75,000/mm^3. The patient, who was found to have a platelet nadir of 25,000/mm^3 during her 1st cycle of therapy at level 3, also developed a constellation of grade 3 nonhematological toxic effects. This was the only individual who required a platelet transfusion during the study. No patients received growth factors for granulocyte support.

Nonhematological Toxicity. Table 4 summarizes the nonhematological toxic effects observed during the first 2 cycles of therapy at each dose level. The majority of these were grades 1 and 2; no patient manifested grade 4 toxicity. Nausea, vomiting, and muscle and joint aches were common but mild. Skin toxicity was also mild, consisting of dry skin or localized vesicular or pustular rash. Alopecia was universal. Peripheral neuropathy, absent at the lower dose levels, was common with higher doses, appearing in 11 of 12 patients treated at levels 2 and 3. The neuropathy occurred in a typical stocking/glove distribution and was manifested by numbness or pain. Six patients with peripheral neuropathy developed peri-oral numbness as well. As described above, the most severe nonhematological adverse effects occurred in 2 patients at dose level 3, consisting of a complex of peripheral neuropathy, stomatitis, and superficial keratopathy, all grade 3.

A variety of ocular side effects was observed, the severity of which appeared to be dose dependent. One patient, entered at level 0, complained of dry eyes but noted no visual disturbance. No ocular complaints were registered by patients treated at level 1. Four patients developed ocular toxicity at level 2. One noted intermittent “smoky” vision, and another experienced blurred vision, both occurring with cycle 1 and both presenting as grade 1. Two other patients at dose level 2 noted “flashing lights” and photosensitivity during their third course of treatment. One went on to develop grade 2 superficial keratopathy during course 4. The other experienced a reversible decrease in visual acuity without specific abnormalities on ophthalmologic exam. At level 3, 2 patients complained of mild dry eyes throughout

Table 4 Nonhematologic toxicity by dose level[a]

	Level 0 (n = 4)		Level 1 (n = 3)		Level 2 (n = 6)		Level 3 (n = 6)	
Toxicity	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3	Grade 1 or 2	Grade 3
Sensory neuropathy	0	0	0	0	4	1	3	3
Ocular	1	0	0	0	2	0	2	2
Stomatitis	0	0	1	0	4	0	3	2
Nausea	1	0	1	0	3	0	4	1
Vomiting	1	0	1	0	0	0	2	1
Diarrhea	1	0	2	0	3	0	1	1
Arthralgia/myalgia	3	0	3	0	4	0	4	1
Skin	0	0	0	0	5	0	2	0
Fever (non-neutropenic)	0	0	0	0	2	0	3	0

[a] Expressed as the number of patients experiencing the toxic effect during the first two cycles of treatment.

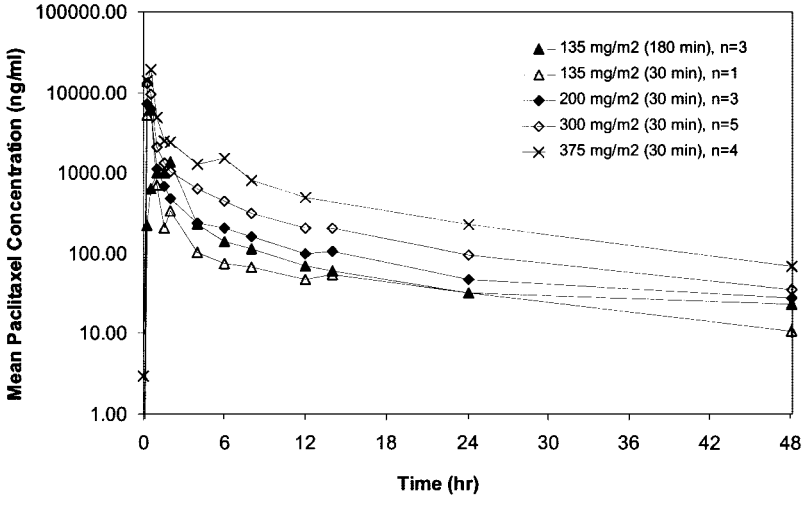

Fig. 1 Pharmacokinetic profile of ABI-007 showing mean whole blood paclitaxel concentrations at increasing doses of ABI-007 *versus* time. All infusions were given over 30 min except for the first 3 patients who received 135 mg/m^2 over 180 min.

therapy but did not experience visual disturbances. Two other patients at dose level 3 developed grade 3 superficial keratopathy during their 1st cycle of treatment, as described above. All cases of keratopathy received full ophthalmologic evaluation, and all resolved with the use of topical lubricating drops and ointments. No patient developed a permanent loss of vision or experienced any other permanent ocular sequellae.

Occurrences of new types of toxic effects after the first 2 cycles of therapy were rare. Furthermore, it was uncommon for toxic effects to increase in grade after the first 2 treatment cycles. Therefore, cumulative toxicity did not appear to be a significant problem.

Response. Partial responses were observed in two breast cancer patients, both of whom had prior exposure to Taxol. The first patient, entered at dose level 2, experienced a 68% decrease in the size of pulmonary metastases. This response lasted a total of 15 months, including 9 months after discontinuation of therapy for toxicity. The 2nd patient, who was also treated at dose level 2, had significant improvement in soft tissue disease involving the chest wall. Because of toxic effects, she was taken off treatment on the date of her response. Disease progression was noted 6 weeks later.

Pharmacokinetic Studies. Sixteen of the 19 patients entered into the study contributed analyzable pharmacokinetic profiles. Three of these received ABI-007 as a 180-min infusion; the remaining 13 were treated over 30 min. A semilog plot of the mean values of the whole blood paclitaxel concentration for each dose level *versus* time is shown in Fig. 1. The maximum paclitaxel concentrations were observed at the termination of ABI-007 infusion; the decline from maximum was biphasic.

A summary of the pharmacokinetic parameter values derived by noncompartmental methods is shown in Table 5. The pharmacokinetics of ABI-007 administered over 30 min appeared to be linear across the three lower dose levels, which included the MTD (Fig. 2). Calculations from the data in Table 5 reveal a 2.2-fold increase in C_{max} and a 2.7-fold increase in AUC_{inf} over the 2.2-fold increase in dose from 135 to 300 mg/m^2. The decline in CL estimates over this range is 0.8-fold (16.1%). If the highest dose level of 375 mg/m^2 is included, nonlinearity becomes evident (Fig. 2). Individual C_{max} and AUC_{inf} values *versus* dose are shown in Fig. 3, *a* and *b*, respectively.

The group of 13 patients who received 30-min infusions and for whom pharmacokinetic profiles were obtained included 3 who experienced grade 3 nonhematological toxic effects (neuropathy with or without stomatitis and keratopathy). The C_{max} and AUC_{inf} for these 3 patients relative to those of the remaining 10 patients are plotted in Fig. 4. The differences in mean C_{max}

Table 5 Summary of noncompartmental pharmacokinetic parameters, mean (% coefficient of variation) values by dose[a]

Dose mg/m^2	Infusion duration min	*n*	C_{max} ng/ml	AUC_{inf} ng/h/ml	Half-life h	CL liter/h/m^2	V_z liter/m^2
135	180	3	1392 (30)	5654 (42)	12.9 (60)	27.4 (45)	418 (32)
135	30	1	6100	6427	14.6	21.1	442
200	30	3	7757 (35)	9613 (20)	13.4 (67)	21.4 (21)	384 (64)
300	30	5	13520 (7)	17610 (21)	14.6 (14)	17.7 (22)	370 (23)
375	30	4	19350 (15)	35805 (40)	13.2 (12)	11.9 (42)	236 (54)

[a] *n*, number of patients; C_{max}, maximum or peak concentration; AUC_{inf}, area under the whole blood/plasma concentration-time curve from time 0 to time infinity; CL, total body clearance; V_z, volume of distribution.

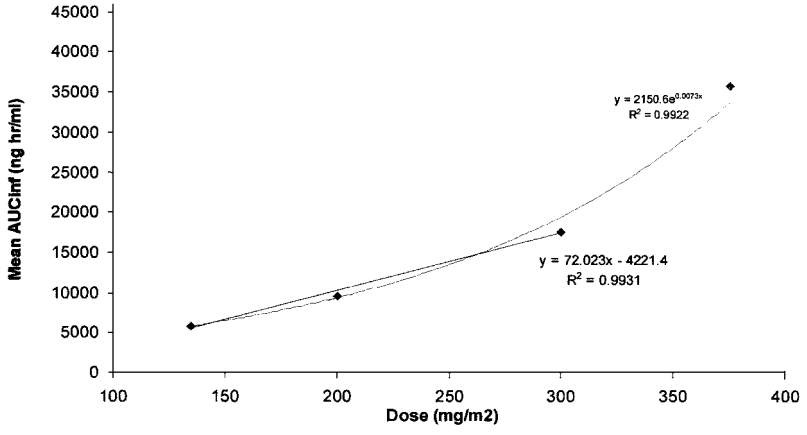

Fig. 2 Correlation between the mean AUC_{inf} and dose level. The data have been fit using a linear regression and an exponential regression function.

and mean AUC_{inf} between the two groups were significant (P = 0.034 and 0.007, respectively). The effect of ABI-007 exposure on myelosuppression was also examined in this group of patients. The percentage of decrease in ANC from baseline to nadir was found to correlate positively with both C_{max} (r = 0.610, P = 0.027) and AUC_{inf} (r = 0.614, P = 0.025).

DISCUSSION

This clinical trial was conducted to examine the pharmacokinetic properties and spectrum of toxic effects associated with ABI-007. Because ABI-007 is not formulated in a Cremophor-containing solvent, we anticipated that hypersensitivity reactions would be diminished or absent. Our results show that ABI-007 can indeed be administered safely as a short infusion without dexamethasone or antihistamine premedication. Thus, when considering the process of drug administration, ABI-007 appears to offer advantages in terms of safety (avoidance of hypersensitivity reactions), morbidity (avoidance of dexamethasone premedication), and patient convenience and comfort (less time spent in the treatment center). These advantages could ultimately translate into an overall decrease in cost of therapy.

It must be pointed out that, although the absence of Cremophor is clearly desirable with respect to toxicity, this same compound has been proposed to enhance the efficacy of cytotoxic drugs through reversal of the multidrug resistance phenotype (15). Plasma concentrations of Cremophor attainable during Taxol infusions are sufficient to inhibit P-glycoprotein effects *in vitro* (16). However, there have been questions raised as to whether these Cremophor concentrations are relevant to solid tumors, as pharmacokinetic studies demonstrate the compound's distribution to be limited to the central plasma compartment (17). This issue should be clarified with the completion of ongoing Phase II trials of ABI-007. If the response rate of ABI-007 is not less than that of Taxol and if responses are seen in patients who are previous taxane failures, the therapeutic contribution of Cremophor to paclitaxel can be considered negligible.

In terms of treatment-related toxicity, a lower incidence of myelosuppression was observed than that which we anticipated based on the dose of paclitaxel administered. In this regard, hematological toxicity was mild and played virtually no role in dose and treatment decisions made in this trial. Although direct comparisons to Taxol administered at this dose range and schedule are not possible, the myelosuppression induced by ABI-007 appeared to be similar to or less severe than that reported for 1-h Taxol infusions at lower doses (18). Otherwise, the spectrum of toxic effects produced by ABI-007 resembled that of high-dose short-infusion Taxol reported in early Phase I trials, with sensory neuropathy and mucositis becoming dose limiting (19, 20). A third dose-limiting toxic effect, superficial keratopathy, was also observed. We were unable to find any prior report of superficial keratopathy as a consequence of paclitaxel administration. In our Phase I trial, this side effect appeared to be related to dose and presented at the level of grade 3 only above the MTD, at a dose of 375 mg/m^2. Superficial keratopathy secondary to ABI-007 was similar to that most commonly recognized in association with 1-β-D-arabinofuranosylcytosine, although any type of ocular surface irritation, including dry eye syn-

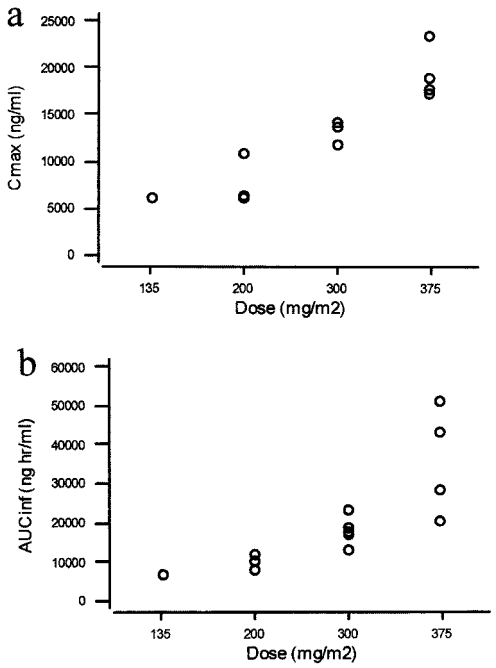

Fig. 3 Individual values of C_{max} (*a*) and AUC_{inf} (*b*) *versus* dose for patients receiving 30-min infusions of ABI-007.

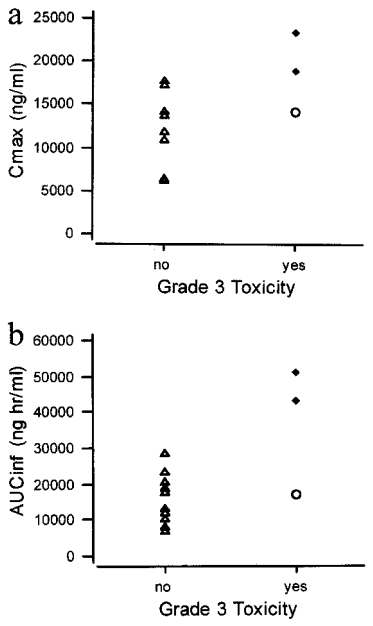

Fig. 4 Individual values of C_{max} (*a*) and AUC_{inf} (*b*) for patients who experienced grade 3 nonhematological toxic effects ("yes") and those who did not ("no"). In the "yes" category, the solid diamond symbols (♦) represent 2 patients with multiple grade 3 toxicities, whereas the open circle (○) represents the patient with only grade 3 neuropathy.

drome, can result in similar corneal findings (21). Other ocular complications of taxane therapy have been reported. The most common adverse ocular effects of Taxol are photopsia and blurred vision, usually reported by patients during the infusion period (22, 23). Cases of optic nerve disturbances have also been documented (24). Cases of grade 2 conjunctivitis necessitating dose reduction and treatment delay have been reported during weekly therapy with docetaxel (25). Similar to our findings, reported ocular effects from paclitaxel have been noted only at higher doses and are usually transient. Although all cases of keratopathy in this study resolved completely and without permanent sequellae, in the ensuing Phase II trial, patients will be aggressively monitored for the development of ophthalmologic abnormalities.

Pharmacokinetic analysis of ABI-007 revealed interesting similarities and differences relative to Taxol, based on published data. Disappearance from the blood is biphasic for both drugs (19). ABI-007 displays linear pharmacokinetics over the clinically relevant dose range of 135–300 mg/m^2; over a similar dose range, Taxol AUC_{inf} is nonlinear (26–28). In comparing the AUC_{inf} values of ABI-007 infused over 30 min to those reported for Taxol infused over 1 or 3 h, ABI-007 in general showed lower AUC_{inf} values over a similar range of doses (26–28). Although several explanations are possible for the differences in AUC_{inf}, it is reasonable to hypothesize that ABI-007 may be distributed more rapidly out of the vascular compartment, a suggestion supported by the difference in formulation between the two drugs. A substantial amount of solvent (Cremophor/ethanol) is infused with Taxol, and the partition of paclitaxel from the vascular compartment to the tissues may thus be relatively slow. In contrast, ABI-007 is formulated with human serum albumin at a concentration of 3–4%, similar to the concentration of albumin in the blood. Because paclitaxel has a very limited solubility in an aqueous albumin solution (<30 μg/ml), it may partition more efficiently into the tissues in the case of ABI-007. Furthermore, lipid, macromolecular, and nanoparticle drug carriers have been known to preferentially accumulate in tumor beds and tissues in what is known as enhanced permeation and retention effect (29). These factors may facilitate the partition of ABI-007 into tissues.

The MTD of ABI-007 was found in this study to be 300 mg/m^2 when given as a short infusion on a 21-day cycle. Although the usual dose range for Taxol is 135–200 mg/m^2, doses as high as 250 mg/m^2 are occasionally administered. Therefore, the MTD established by this trial represents a moderate increase over that of Taxol. The issue of whether one can achieve uniform and repeated dosing of ABI-007 at the MTD will need to be addressed in Phase II trials.

In conclusion, ABI-007 appears to represent an improvement in paclitaxel formulation in that it can be administered rapidly and safely without the risk of hypersensitivity reactions, eliminating the need for steroid and antihistamine premedication. Furthermore, the increased MTD and favorable toxicity profile of ABI-007 may ultimately prove advantageous in terms of rate and quality of response. Although several interesting pharmacokinetic properties were noted for ABI-007, the small number of patients in this study renders comparisons with Taxol preliminary, and additional studies will need to be conducted to fully appreciate differences in pharmacokinetic behavior. The partial responses seen in 2 patients with prior exposure to Taxol are encouraging and support a continued effort to explore the

spectrum of activity for this drug. We are currently conducting a Phase II trial of ABI-007 for patients with metastatic breast cancer to establish the antitumor activity of this novel paclitaxel formulation.

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Intraarterial Chemotherapy with Polyoxyethylated Castor Oil Free Paclitaxel, Incorporated in Albumin Nanoparticles (ABI-007)

Phase I Study of Patients with Squamous Cell Carcinoma of the Head and Neck and Anal Canal: Preliminary Evidence of Clinical Activity

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BACKGROUND. This study was designed to determine the feasibility, maximum tolerated dose, and toxicities of intraarterial administration of paclitaxel-albumin nanoparticles in patients with advanced head and neck and recurrent anal canal squamous cell carcinoma. Antitumor activity also was assessed.

METHODS. Forty-three patients (31 with advanced head and neck and 12 with recurrent anal canal squamous cell carcinoma) were treated intraarterially with ABI-007 every 4 weeks for 3 cycles. In total, 120 treatment cycles were completed, 86 in patients with head and neck carcinoma (median, 3 cycles; range, 1–4) and 34 in patients with anal canal carcinoma (median, 3 cycles; range, 1–4). ABI-007 was compared preliminarily with Taxol® for in vitro cytostatic activity. Increasing dose levels from 120 to 300 mg/m^2 were studied in 18 patients. Pharmacokinetic profiles after intraarterial administration were obtained in a restricted number of patients.

RESULTS. The dose-limiting toxicity of ABI-007 was myelosuppression consisting of Grade 4 neutropenia in 3 patients. Nonhematologic toxicities included total alopecia (30 patients), gastrointestinal toxicity (3 patients, Grade 2), skin toxicity (5 patients, Grade 2), neurologic toxicity (4 patients, Grade 2) ocular toxicity (1 patient, Grade 2), flu-like syndrome (7 patients, Grade 2; 1 patient, Grade 3). In total, 120 transfemoral, percutaneous catheterization procedure–related complications occurred only during catheterization of the neck vessels in 3 patients (2 TIA, 1 hemiparesis) and resolved spontaneously.

CONCLUSIONS. Intraarterial administration of ABI-007 by percutaneous catheterization does not require premedication, is easy and reproducible, and has acceptable toxicity. The maximum tolerated dose in a single administration was 270 mg/m^2. Most dose levels showed considerable antitumor activity (42 assessable patients with 80.9% complete response and partial response). The recommended Phase II dose is 230 mg/m^2 every 3 weeks. ***Cancer* 2001;92:2592–602.**

KEYWORDS: taxanes, paclitaxel, intraarterial chemotherapy, squamous cell carcinoma.

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Paclitaxel was the first taxane to be introduced into clinical practice, but because of its poor solubility in water it must be formulated with polyoxyethylated castor oil and ethanol (Taxol®). Polyoxyethylated castor oil can cause allergic reactions; therefore, patients must receive premedication with dexamethazone, diphenhydramine, and cimetidine before paclitaxel administration. In addition, special precautions for the intravenous administration set are necessary, and it is advisable for infusion to be given over 3–24 hours.[1,2] Despite these measures, severe hypersensitivity reactions are reported in 1.5–3% of patients, and more modest reactions are observed in almost half of patients.[3] A recently published article highlights this problem and suggests changing patients with allergic reactions to another taxane, docetaxel.[4]

Intraarterial administration of taxanes has been considered only sporadically up to now.[5,6] The presence of alcohol in the commercial formulation and the problem of hypersensitivity reactions represent an obstacle to administration by this route, unless the drug is diluted considerably. A new polyoxyethylated castor oil free formulation of paclitaxel provided the opportunity to assess intraarterial chemotherapy with this cytostatic agent in squamous cell carcinomas of the head and neck and of the anal canal.

Few studies have been conducted to date on the activity of systemically administered taxanes in advanced head and neck carcinoma. In these studies, intravenous paclitaxel as a single agent has shown superior activity to that of the standard combined chemotherapy (cisplatin, 5-fluorouracil) in recurrences of these cancers, but the improvement was not very great. Overall, when more recent taxanes such as docetaxel are included, objective response rates (complete and partial clinical-radiologic) range from 30% to 42% in recurrences.[7–9]

Less than 30% of patients with locally advanced disease (American Joint Committee on Cancer [AJCC] TNM Stage III/IV) can be cured with surgery and/or radiotherapy. The chemotherapy regimen that achieves a complete clinical response of 30–50% and greater is the combination of cisplatin and fluorouracil given at initial presentation of the disease. Combination with radiotherapy improves the results but at the cost of greater toxicity.[10–12] Despite this result, neoadjuvant chemotherapy has not brought an improvement in survival, which depends more on locoregional recurrence than on distant metastases. A high T classification makes local recurrence more likely and is less amenable to clinical response and even less to complete pathologic response. Efforts to improve the results of neoadjuvant chemotherapy in advanced carcinoma of the oral cavity and hypopharynx are justified by the possibility of achieving definitive local treatment by surgery or radiotherapy while maintaining an acceptable quality of life, including organ preservation.

FIGURE 1. Electron microscope enlargement (original magnification ×34,000) of paclitaxel-albumin nanoparticles (ABI-007).

Cystostatic drugs have been given by intraarterial administration in the past, particularly since the introduction of cisplatin. The responses reported (clinical-radiologic, complete, and partial) range from 47% to 94% in patients with miscellaneous advanced disease at presentation or with recurrence. The rate of catheter-related complications was greater than 30%.[13–16]

The expansion of interventional neuroradiology techniques, which now have high reproducibility and an acceptable complication rate, has led to the availability of new materials for superselective catheterization, prompting renewed interest in intraarterial chemotherapy of the cervicofacial district.[17–19] However, in this reappraisal of intraarterial chemotherapy, the drugs used thus far have been the same as in the past, and in no case have taxanes been used.

ABI-007 is a new formulation of paclitaxel. Its novelty lies in the use of human albumin as a stabilizer in place of the usual excipients, polyoxyethylated castor oil and alcohol. The particles of the paclitaxel-human albumin complex have a dimension of 150–200 nm (Fig. 1), and the product takes the form of a colloid when suspended in saline solution. Animal studies have shown that the pharmacokinetic profile of ABI-007 differs from that of the commercial formulation (Taxol) in that it shows lower plasma levels and higher tissue levels with wider, more rapid distribution and slower metabolism. ABI-007 is 59-fold less toxic than Taxol and 29-fold less toxic than the excipients of Taxol.[20] Preliminary results of clinical intravenous and intraarterial use were presented recently.[21,22]

The decision to study intraarterial chemotherapy

with paclitaxel in albumin nanoparticles in patients with squamous cell carcinoma of the head and neck and of the anal canal was based on consideration of the mechanism of action of this drug and of the particular problems posed by these two carcinomas. The antitumor efficacy of paclitaxel is related to its ability to stabilize microtubules. Alterations of microtubule dynamics may be of relevance not only in the mitotic spindle, but also in cytoskeleton functions. Because cytoskeleton is involved in signaling pathways mediated by growth factor receptors, the pharmacologic effects of taxanes could be at least in part caused by their interference with signal transduction. Because squamous cell carcinomas of different tissue origin (lung, head/neck, cervix) are characterized by overexpression of epidermal growth factor (EGF) receptors, the efficacy of paclitaxel in the treatment of these tumor types could reflect an interference of this taxane in specific processes mediated by growth factor receptors. This hypothesis should be addressed by specific approaches of modulation of receptor function. A better documentation of this additional molecular effect could allow a more rational design of clinical studies with taxanes.[23]

Squamous cell carcinoma of the anal canal has a high curability rate at presentation when treated by a combination of chemotherapy, radiotherapy, and surgery, but no further systemic therapeutic regimen is available for effective management of recurrence.[24,25] The rationale of intraarterial administration is reinforced in this pathology by the critical nature of pelvic vascularization due to the previous treatments, which might make it difficult to achieve an effective local concentration of systemically administered cytostatic agents.

The principal goals of the current study were 1) to determine the feasibility of intraarterial administration of ABI-007, 2) to determine the maximum tolerated dose (MTD), 3) to determine the dose-limiting toxicity, 4) to establish the recommended dose for a Phase II study, and 5) to seek preliminary evidence of antitumor activity.

MATERIALS AND METHODS

Comparative In Vitro Cytotoxic Evaluation of ABI-007 and Taxol

A comparative study of the cytotoxic effects of Taxol and ABI-007 was performed in two human ovarian carcinoma cell lines, including a cell line sensitive to cisplatin (IGROV-1) and a subline selected for resistance to cisplatin (IGROV-1/Pt1), exhibiting a collateral sensitivity to taxane and in a squamous cell carcinoma of the cervix (A431) exhibiting overexpression of the EGF receptor. The cytotoxic activity

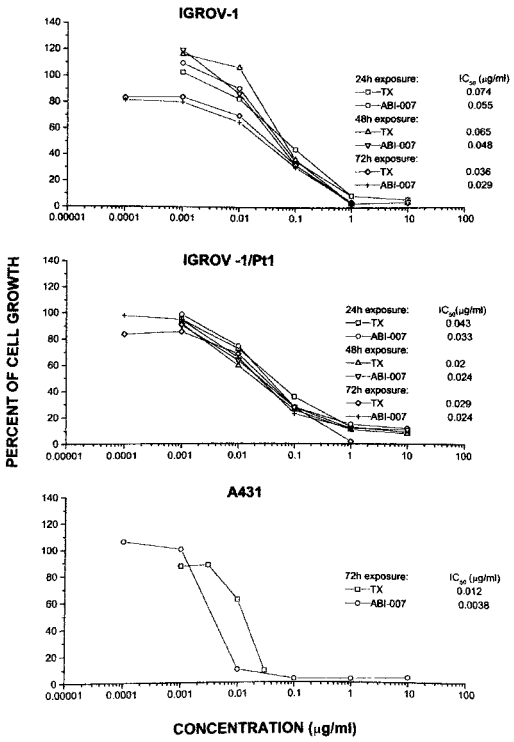

FIGURE 2. Comparison of cytotoxic activity of paclitaxel (TX) and ABI-007 in ovarian cell carcinoma IGROV-1, in a subline selected for resistance to cisplatin IGROV-1/Pt 1 and in cervical squamous cell carcinoma cells. Cells were exposed to the drug for 24, 48, or 72 hours as indicated. The antiproliferative effect was determined by the growth inhibition assay (cell counting 72 hours after the start of exposure). IC_{50} values refer to drug concentrations required for 50% inhibition of cell growth.

was evaluated using an antiproliferative assay (determination of the number of surviving cells 72 hours after drug exposure) and variable exposure times (24, 48, and 72 hours). The cell systems were chosen because the cytotoxic effect of paclitaxel was predictive of antitumor efficacy after in vivo treatment of tumor xenografts in athymic mice.

Because the drug formulation could interfere with cellular uptake of the drug, a comparative cellular pharmacology study was performed to examine the cytotoxic potential of the drug in various formulations using a panel of human tumor cell lines. The results are shown in Figure 2 as dose–response curves. It is evident that the cytotoxic activity of paclitaxel is retained completely in its formulation with albumin. Although the observed difference in cellular response should be regarded as marginal, an increased cytotoxicity of ABI-007 was consistently found in all experiments. A similar result was found in the A431cell line, which exhibited an increased sensitivity to taxanes.

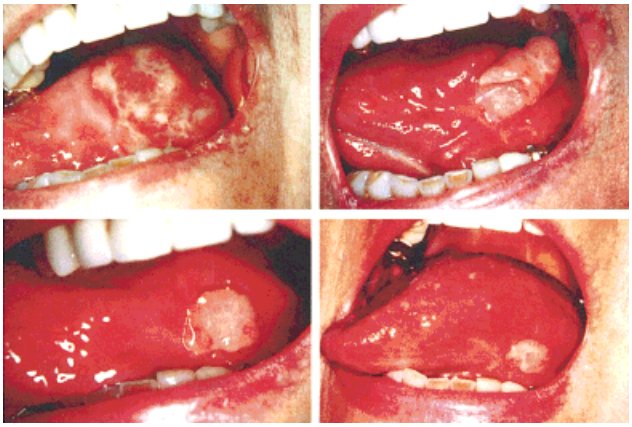

FIGURE 3. Carcinoma of left margin of tongue. At presentation (top left), after one cycle of ABI-007 into the lingual artery (top right), after two cycles (bottom left), after three cycles (bottom right). This patient received a fourth cycle of intraarterial chemotherapy, and no tumor was found at surgery. The patient also underwent total laterocervical lymph node resection with negative histology. The patient was disease free at last follow-up (10 months).

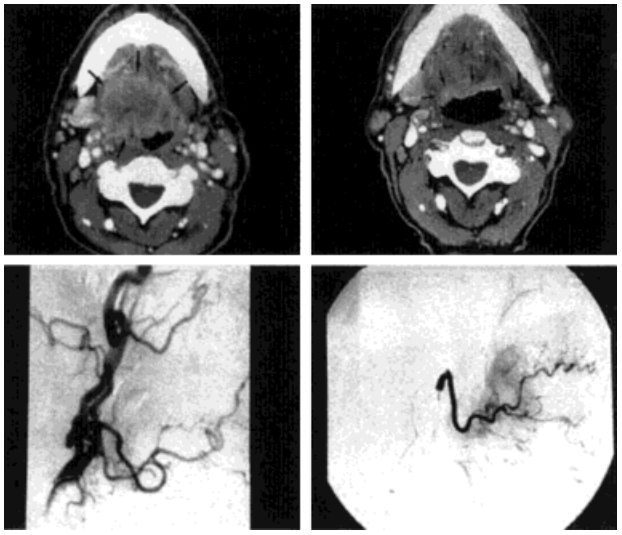

FIGURE 4. Carcinoma of the tongue. Computed tomography with contrast medium (top left); the arrows indicate the tumor margins. Result after three cycles of intraarterial chemotherapy (top right). Angiogram of right common carotid artery (bottom left). Catheterization and angiography of lingual artery (bottom right).

PATIENTS

Patient Selection

Patients considered eligible for this study were 1) those with histologic diagnosis of locally advanced squamous cell carcinoma of the head and neck with or without previous treatment; and 2) patients with recurrent squamous cell carcinoma of the anal canal. Inclusion criteria were age older than 18 years and younger than 75 years; Eastern Cooperative Oncology Group performance status of less than 2; previous chemotherapy, with exclusion of taxanes, completed at least 4 weeks before study enrollment; life expectancy longer than 3 months; and adequate bone marrow (platelet count $> 75{,}000 \times 10^9$ cells/L, absolute neutrophil count $> 1.5 \times 10^9$ cells/L), hepatic function (total bilirubin within normal limits, transaminases < 2 times normal), and renal function (creatinine < 1.5 times the upper limit of normal). Patients with formal contraindications or in whom transfemoral catheterization/angiography was not possible and those with severe cardiopathy were excluded.

Before enrollment in the trial, patients were required to sign the informed consent document to be enrolled in the trial, which was approved by the Ethical and Scientific Committee of the institution.

Dosage and Administration of ABI-007

ABI-007 was supplied by American BioScience, Inc. (Los Angeles, CA) in vials containing a lyophil equal to 30 mg of paclitaxel/albumin. The solution obtained by diluting each vial with 10 mL of 0.9% sodium chloride solution was administered over 30 minutes by selective percutaneous catheterization of the neck vessels in patients with head and neck carcinoma, with access from the femoral artery under local anesthesia, without premedication. A guiding catheter (Envoy H1 5F; Cordis/Johnson & Johnson, Miami, FL) first was positioned in the common carotid artery for digital angiography. Bilateral catheterization was performed for tumors that exceeded the median line. Intraarterial chemotherapy was performed by selectively or superselectively catheterizing the external carotid artery or its branches with coaxial microcatheters in a guiding catheter (Transit Infusion Catheter; Cordis/Johnson & Johnson).

In patients with recurrence of anal canal carcinoma, unilateral or bilateral transfemoral percutaneous catheterization of the internal iliac arteries was performed (Tempo 4 C3, 4F; Cordis/Johnson & Johnson) after pelvic aortography, with placement of a coaxial microcatheter (Rapid Transit; Cordis/Johnson & Johnson) distal to the gluteal artery. To prevent clotting within the catheter, we used a continuous washing set of our own design produced by SIDAM (Mirandola, Italy). Three treatment cycles were planned for both groups of patients, with a 4-week interval between cycles (in 2 patients 4 cycles were performed). The hospital stay was 3 days for each cycle.

The MTD was defined in this study as the dose level below that inducing dose-limiting toxicity in greater than a third of cycles at the same dose level (at least three cycles of a group of six).

The dose increase scheme was empiric and arbitrarily designed by us.

The starting dose of 120 mg/m^2 was increased by 30 mg/m^2 at each subsequent level. Each level consisted of a group of six cycles. In the first 4 cycles, Grade 4 hematologic toxicity occurred in 3 cases in the group receiving 300 mg/m^2. The MTD therefore was defined as 270 mg/m^2. The total number of cycles "necessary" to define the dose-limiting toxicity and the MTD was 40 (29 cycles for 12 patients with head and neck carcinoma and 11 cycles for 6 patients with carcinoma of the anal canal).

Of the 18 patients participating in dose escalation (5 of whom completed treatment after determination of the MTD, receiving 250 mg/m^2 for the remaining cycles), 1) 8 patients received 3 cycles; 2) 6 patients received 2 cycles (1 discontinued treatment because of progression, 1 withdrew despite evidence of complete clinical response, and 4 received the third cycle at the dose 250 mg/m^2), 3) 4 patients received only 1 cycle (1 completed the treatment at 250 mg/m^2, 2 discontinued it because of progression, 1 patient died after rupture of esophageal varices complicating concomitant cirrhosis).

To better define the importance of the intraarterial chemotherapy procedure and make a preliminary evaluation of the tolerability of the ABI-007 dose to be recommended for Phase II study, we enrolled an additional 19 patients with head and neck carcinoma and 6 with recurrence of anal canal carcinoma. Treatment with 250 mg/m^2 every 4 weeks for 3 cycles was planned for this additional group.

Dose-Limiting Toxicities

All toxicities were graded according to World Health Organization (WHO) toxicity criteria. The MTD, as already stated, was defined as the dose level below that which induced a limiting toxicity in at least three of six cycles. Grade 4 neutropenia lasting 5 days or longer, Grade 4 thrombocytopenia or anemia of any duration, and Grade 3 or 4 nonhematologic toxicities were considered as dose-limiting.

Pretreatment and Follow-Up Studies

Complete clinical history, physical examination, hematologic examination, serum electrolytes, and chemistries were performed at the time of enrollment and before each cycle. Complete blood cell counts were taken weekly while patients were on study. Radiologic studies (computed tomographic scans or magnetic resonance imaging) were performed at baseline and before each treatment cycle to assess tumor response, which was graded according to WHO criteria.

Pharmacokinetic Analyses

To study the pharmacokinetics of ABI-007, extensive blood samples were drawn in 11 patients, from the superior vena cava (5 patients with head and neck carcinoma), from the inferior vena cava (6 patients with anal canal carcinoma), and from peripheral veins (11 patients) at multiple times during each infusion (at 0, 5, 15, and 30 minutes) and up to 18 hours (at 35, 45, 60, 90, 150, 270, 510, 750, and 1080 minutes).

Whole blood paclitaxel concentrations were determined by high-performance liquid chromatography after solid phase extraction, as described by Willey et al.[26] with some modifications. Standard curves were obtained using paclitaxel C (Indena, Milan, Italy) as internal standard. The drug quantitation limit was 0.06 μmol/L and the linearity up to 30 μmol/L with a precision range between 8.1% and 18% and an accuracy that exceeded 85%. The recovery of paclitaxel was 95%. The same method was used to check the paclitaxel contents in administered ABI-007 solutions.

Pharmacokinetic modeling and parameters were performed using the nonlinear regression program Kinetica 2000 version 3.0 (Innaphase Co., Philadelphia, PA). The concentration versus time curves were fitted using a three-compartment open pharmacokinetic model.

The data were compared with pharmacokinetic profiles with intravenous infusion of ABI-007 (Ibrahim NK, Ellehorst JA, Theriault RL, et al. Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel, unpublished).

RESULTS

Thirty-one patients with head and neck carcinoma received a total of 86 cycles (median, 3). Twelve patients with recurrent anal canal carcinoma received 34 cycles (median, 3).

Patient characteristics are summarized in Table 1.

Toxicity

Tables 2 and 3 summarize the hematologic and nonhematologic toxicities of all grades observed in 12 patients with squamous cell carcinoma of the head and neck and in 6 patients with squamous cell carcinoma of the anal canal who participated in dose escalation to define the MTD of intraarterial chemotherapy with ABI-007.

Neutropenia was the main dose-limiting toxicity for intraarterial administration of paclitaxel. Of the three episodes recorded, two were short-lasting and did not require hospitalization. These episodes occurred in two patients with recurrent anal canal car-

TABLE 1
Patient Characteristics

Characteristic	Total	Head and neck carcinoma	Anal canal carcinoma
No. of patients	43	31	12
Gender			
Male	27	25	2
Female	16	6	10
Age, median (range)	58 (36–75)	63 (36–75)	56 (41–75)
Previous treatment			
Surgery + CHT + RT		5	5
CHT + RT		1	5
Surgery + RT		3	—
Surgery		1	2
CHT		2	—
RT		1	—
None		17	—
Surgery + CHT		1	—
Tumor site			
Tongue		10	—
Maxillary sinus		2	—
Floor of mouth		1	—
Soft tissues of the neck		5	—
Laryngopharynx		3	—
Overlapping lesion of oro/ hypopharynx		1	—
Larynx		1	—
Piriform sinus		1	—
Retromolar trigone		2	—
Oropharynx		2	—
Overlapping lesion of tonsil and palate		3	—
Lower pelvis		—	12

CHT: chemotherapy; RT: radiation therapy.

TABLE 2
Hematologic Toxicity

		Cycles with neutropenia/grade							
		Head and neck (grade)				Anal canal (grade)			
Dose (mg/m^2)	Total no. of cycles	1	2	3	4	1	2	3	4
120	6	4							
150	6	2							
180	6	4							
210	6	2	1						
240	6						1		
270	6	1	1			2			
300	4				1				2

cinoma who previously had been treated with radiation therapy (RT) and chemotherapy and with chemotherapy plus RT plus surgery, respectively. The third case was a patient with metastatic carcinoma of the head and neck from an unknown primary site, previously treated with RT and surgery and who also had cirrhosis with esophageal varices. The patient was admitted to the hospital because of rupture of the varices 6 days after intraarterial chemotherapy and died of esophageal bleeding.

Neutropenia never was associated with infection, occurred approximately 8 days after the chemotherapy, and resolved within a week in the 2 assessable cases. At a dose of 270 mg/m^2, Grade 4 neutropenia occurred in 1 previously untreated patient with carcinoma of the head and neck. Grade 2 neutropenia occurred in 15.7% of patients in the series with tumors of the head and neck treated with 250 mg/m^2, and in 33.3% in the much smaller series of patients with recurrent anal canal carcinoma.

The most important nonhematologic toxicities from the point of view of their impact on the quality of life were neuropathy lasting approximately 2 weeks, flu-like syndrome (of shorter duration), and ocular toxicity (keratitis). All these toxicities, which were in any case of low grade, occurred in few patients treated at the dose of 250 mg/m^2 (Table 4).

Procedural Complications

Of 120 percutaneous catheterizations, 3 complications (2.5%) were observed in 3 patients during catheterization of the neck vessels for infusion of ABI-007. These complications were two transient ischemic attacks and one hemiparesis, the latter resolving within a few days. The patient who had the hemiparesis previously had undergone surgery, including radical bilateral neck dissection, chemotherapy, and RT. The two cerebral transient ischemic attacks occurred in two patients who had received previous treatment, one RT and one chemotherapy. In all three cases, the external carotid artery was selectively catheterized by the method described. The accidents occurred at the time of removal of the catheter, most likely due to detachment of debris at the carotid bifurcation, which showed atheromatous plaque in all three cases, particularly in the patient with hemiparesis.

No complications related to the catheterization procedure occurred in the population treated for recurrent anal canal carcinoma.

Antitumor Activity

Forty of 43 patients were assessable for antitumor activity of intraarterial chemotherapy with ABI-007. Three patients (all previously treated with combined regimens) received only one cycle and were not assessable: one died after rupture of esophageal varices complicating cirrhosis and the other two discontinued treatment because of disease progression. The latter two patients were treated with alternative chemotherapy regimens without success.

TABLE 3
Nonhematologic Toxicity for Head and Neck Carcinoma and Anal Canal Carcinoma

Dose (mg/m²)	Total no. of cycles	Neuropathy (grade)				Gastrointestinal (grade)				Flu syndrome (grade)				Ocular (grade)				Cutaneous (grade)				Alopecia (grade)			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Head and neck carcinoma																									
120	6	2				2				2				4					3			1	3		
150	6										1												3		
180	5	1	1			2				4	1							1					4		
210	5	3				1	1			2	1	1		1	1			1					5		
240	2					1	1			2					1			1					2		
270	3	3								2													2		
300	2					1																	1		

Dose (mg/m²)	Total No. of Cycles	Neuropathy				Gastrointestinal				Flu syndrome				Cutaneous				Alopecia			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Anal canal carcinoma																					
120	—																				
150	—																				
180	1																				
210	1									1									1		
240	4		1				2			2	2								3		
270	3						1			2				2					3		
300	2			1						1	1								1		

TABLE 4
Hematologic and Nonhematologic Toxicity in 25 Patients Treated Intraarterially with ABI-007 at a Dose of 250 mg/m² (Total of 80 Cycles, Median 3)

Characteristic	Total	Head and neck cancer	Anal canal cancer	Grade				Grade			
				1 (%)	2 (%)	3 (%)	4 (%)	1 (%)	2 (%)	3 (%)	4 (%)
No. of patients	25	19	6								
Gender											
Female		3	5								
Male		16	1								
Age, median (range)		64 (36–72)	57 (41–64)								
Hematologic toxicity				47.3	15.7			50.0	33.3		
Nonhematologic toxicity											
Alopecia				6	12			16.6	83.3		
Gastrointestinal				7	1			1	1		
Flu-like syndrome				7	3			3	3		
Cutaneous				1	2				1		
Ocular				1							
Neurologic				4	1			2	1		

Of the 40 assessable patients, 29 belonged to the head and neck carcinoma group in which there were 3 complete responses (2 pathologic and 1 clinical). The three patients had received no previous treatment and were treated with radical surgery (1 patient with carcinoma of the tongue who had received 4 cycles), with radical neck dissection and radiotherapy (1 patient with carcinoma of the piriform sinus), and with surgery and radiotherapy (1 case of carcinoma of the retromolar trigone).

Nineteen partial responses were observed in head and neck carcinomas (6 previously treated patients and 13 not previously treated). The sum of complete and partial responses was 75.85% (complete response,

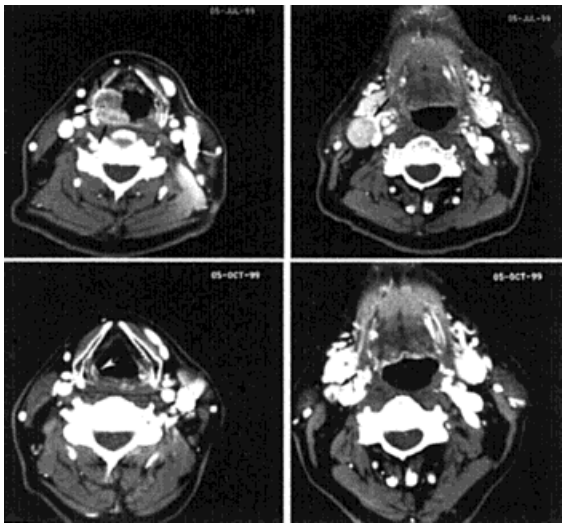

FIGURE 5. Carcinoma of right piriform sinus. Computed tomography (CT) of pharynx/larynx with arrows indicating the tumor margins (top left). CT with arrows indicating adenopathy (top right). CT after third cycle of intraarterial chemotherapy (bottom left); arrow indicates the primary tumor site no longer evident at histologic examination. CT of neck also shows a partial response for adenopathy (bottom right).

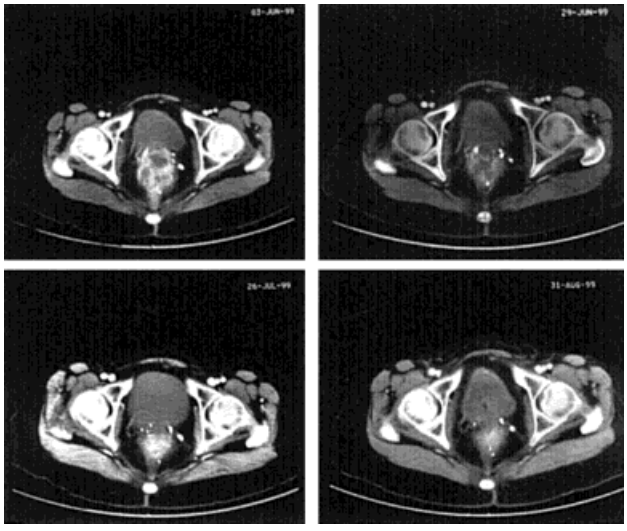

FIGURE 6. Recurrent anal canal carcinoma. Computed tomography (CT) with contrast medium at presentation (top left). CT after first cycle of chemotherapy via the internal iliac arteries (top right). CT after second cycle (bottom left). CT after third cycle (bottom right). It is not possible with imaging alone to determine whether tumor is still present. No tumor was found at surgery. The patient was disease free at last follow-up (4 months).

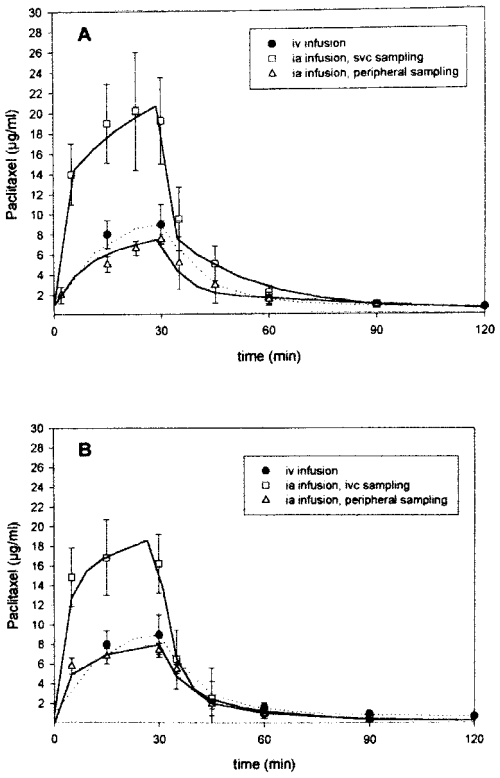

FIGURE 7. (A and B) Mean paclitaxel concentration versus time profiles in patients with head and neck (A) or anal canal (B) carcinomas during and after 30-minute constant infusion of ABI-007 (250 mg/m^2 of paclitaxel). The dotted line in each panel represents the profile of an intravenous injected dose. iv: intravenous; ia: intraarterial; svc: superior vena cava; ivc: inferior vena cava.

10.34%; partial response, 65.51%; Figs. 3–5). The six previously treated patients were offered alternative chemotherapy. Of the 13 not previously treated, 9 received surgery after intraarterial chemotherapy, 1 chemotherapy, 1 RT, and 2 RT and chemotherapy. Six of the remaining seven assessable patients had received previous treatment, and of these one progressed, four had stable disease, and one developed a massive tumor necrosis with fistulization after the second cycle of intraarterial chemotherapy, and therefore treatment was discontinued. The last patient, not previously treated, showed stable disease.

In the 22 responding patients, the median duration of follow-up for patients who had not received previous treatment was 12 months (range, 3–13 months); for previously treated patients, the median was 5 months (range, 3–13 months).

Twelve previously treated patients belonged to the group with recurrent anal canal carcinoma. Eleven of these were assessable; one patient received only one cycle and showed progression. Three complete responses were recorded, two pathologic and one clinical. One patient with pathologic complete response received four cycles of ABI-007 (Fig. 6); the patient with clinical complete response received two cycles after which she refused to continue treatment because she wished to be reoperated on as soon as possible. Four patients showed partial response, three previ-

TABLE 5
ABI-007 Pharmacokinetic Parameters

Cancer type	Administration	Sampling	Paclitaxel (mg/m^2)	No. of patients	Cmax (mg/L)	Tmax (min)	$T_{1/2}\ \alpha$ (min)	$T_{1/2}\ \beta$ (min)	$T_{1/2}\ \gamma$ (min)	AUC (mg/L min)	Vss (L)	Cl (L/min)
Head and neck	i.a. infusion	Superior vena cava	250	5	21.01 (6.5)	30	0.45	15.13	560.59	1146.0 (280)	107.55 (85)	0.338 (0.18)
	i.a. infusion	Peripheral vein	250	5	7.53 (1.8)	30	3.42	38.35	764.67	753.52 (150)	345.55 (45)	0.536 (0.09)
Anal canal	i.a. infusion	Inferior vena cava	250	6	18.58 (5.9)	30	1.94	13.61	529.47	872.29 (210)	114.86 (73)	0.445 (0.1)
	i.a. infusion	Peripheral vein	250	6	7.45 (2.6)	30	3.066	14.64	530.22	548.58 (120)	244.56 (58)	0.707 (0.21)
Solid tumors	i.v. infusion	Peripheral vein	250	8	9.944 (3.1)	30	7.35	114.88	932.87	761.86 (140)	312.27 (40)	0.509 (0.12)

AUC: area under the curve; i.a.: intraarterial; i.v.: intravenous.

ously treated with chemotherapy and RT and 1 with surgery. The remaining four patients (36.36%) showed stable disease. All assessable patients had surgical control (reoperation in six cases). The median duration of follow-up in responding patients (7 cases) was 10 months (range, 7–13 months).

Pharmacokinetics

The concentration/time curve calculated on samples from the superior vena cava and peripheral veins is shown in Figure 7 and compared with the profile of the same dose administered by intravenous infusion.

From the three-compartmental model fit the elimination half-time values were lower than with intravenous administration both in patients with head and neck carcinoma and in those with anal canal carcinoma (Table 5). The mean plasma peak of central venous samples also was observed to be approximately double the corresponding levels obtained with intravenous infusion. This also is reflected in a significant decrease in total clearance.

The plasma curve of the peripheral samples shows a reduced Cmax, and overall clearance was greater than with intravenous infusion. This finding seems to indicate a certain extraction from the administration site.

When the pharmacokinetic values of head and neck carcinoma patients are compared with those of anal canal carcinoma patients, a higher area under the curve value is noted in the former, and this was evident particularly in the central samples. These data are entirely preliminary and a larger series is needed to define the pattern of local extraction. However, on the basis of the clearance value and the selectivity of administration, locoregional treatment can be expected to show a marked advantage.[19]

DISCUSSION

Despite evidence of significant objective responses in many patients, intraarterial chemotherapy has failed to find a place in the therapeutic armamentarium for various cancers and various sites. The responses achieved are caused by the greater first-pass exposure of the tumor to the cytostatic agent, which is a function of plasma clearance of the drug and of the blood flow through the tumor bed. Thus, the more selective the administration into the tumor feeding arterial branches, the greater the exposure to the cytostatic agent. This goal now can be attained, but the progress made to date has not led to an improvement in survival because of the propensity of tumors to develop resistance, which can depend on several factors. There are essentially two mechanisms for overcoming drug resistance: higher doses and drug combinations. Not many drugs are suitable for intraarterial administration, and the pharmacokinetic data available for locoregional treatment are scarce and unreliable.

Evaluations of intraarterial treatment therefore are still empiric, being based on local toxicity, systemic toxicity, and evidence of antitumor activity, as shown by an objective response.

Theoretically at least, intraarterial administration intrinsically has the best characteristics for exposing the tumor to the highest possible drug dose with the likelihood of lower systemic toxicity, whereas local toxicity depends on the accuracy of administration and the properties of the drug.

Squamous cell carcinomas are considered highly responsive tumors. It has been shown recently that, at least for head and neck carcinomas, a better response is achieved with intraarterial administration of cisplatin at doses never reached previously with intravenous treatment.[19] Now that the technical problem of reaching the anatomic treatment site through percutaneous catheterization with high reproducibility and low mor-

bidity has been largely overcome, a synergism with radiotherapy or with other drugs can be expected to give further impulse to the renewed research effort in this direction. Nor will it be long before the development of effective sealants for vascular wall puncture sites makes it possible to offer therapeutic arterial catheterization on an outpatient basis.[27]

A new polyoxyethylated castor oil and alcohol free formulation of the taxane paclitaxel has shown less systemic toxicity in preliminary clinical trials than commercially available formulations and is well tolerated locally even at high concentrations. We therefore felt it should be feasible to expand the possible applications of intraarterial chemotherapy, limiting our attention for the moment to squamous cell carcinomas.

Taxanes have shown promising results in head and neck carcinomas when administered intravenously. Their mechanism of action is different from that of cisplatin, and if the feasibility of intraarterial use were to be confirmed, a synergistic action with cisplatin as well as with radiotherapy would be possible and potentially useful. ABI-007 seems even easier to use in chemotherapy via the branches of the carotid artery than cisplatin. Practically the same dose used in systemic treatments can be administered in 30 minutes through microcatheters without any need for premedication, hydration, antiemetics or steroids and sodium thiosulphate as reported for cisplatin. There are no consequences if paclitaxel-albumin passes into the internal carotid artery. No neurotoxicity has been observed in a study currently under way on the treatment of glioblastomas with the same product, even when ABI-007 was infused selectively into the branches of the internal carotid artery at the dose of 270 mg. Systemic, hematologic, and nonhematologic toxicity was acceptable. As reported in other studies, objective responses are more prevalent in patients who have not received previous treatment. The two patients with complete pathologic responses belonged to this category.

As far as recurrent anal canal carcinomas are concerned, the antitumor activity observed in this study, which was designed primarily to determine feasibility and local and systemic toxicity, was all the more significant in that the patient population studied had received previous treatment, usually combined therapy (10 of 12 patients). The two complete pathologic responses were observed in two patients previously treated with RT and chemotherapy and surgery and RT and chemotherapy, respectively.

Intraarterial administration appears particularly attractive in the pelvic area, especially in previously treated patients. Surgery and radiotherapy, together with the fibrosis that occurs during the healing process, are known to impair local vascularization, making it difficult to expose recurring tumors to drugs given systemically. Because the pelvic arterial district does not pose critical procedural problems, perfusion with a locally tolerated drug can be performed with an occlusive technique (stop-flow), thus greatly increasing tissue concentrations. Furthermore, the considerable clearance value (intravenous total clearance , 509 mL/minute) positions ABI-007 among the drugs that are potentially advantageous in locoregional treatment.[28]

The recommended dose for the Phase II trial in head and neck carcinoma is 230 mg/m^2 every 3 weeks. The manageability, rapid response, and minimal local and systemic toxicity of ABI-007 lead us to expect this new trial to confirm its potential for use in induction chemotherapy of squamous cell carcinomas before definitive treatment.

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Nanoparticle Paclitaxel Formulation Shows Dose Response in Phase II Trials

■ SAN ANTONIO—A nanoparticle formulation of paclitaxel (see drawing below) used first-line in metastatic breast cancer appears highly active with acceptable toxicity at a dose substantially higher than possible with standard-formulation paclitaxel (Taxol), according to combined results of two phase II studies.

The bioengineered, cremophor-free, albumin-based formulation, called ABI-007, was well tolerated at doses of 300 mg/bbm^2 administered over 30 minutes in the absence of either steroids or G-CSF (Neupogen) prophylaxis, according to results presented in a poster at the 25th Annual San Antonio Breast Cancer Symposium (abstract 522). Lead author of the poster was Nuhad K. Ibrahim, MD, associate professor of breast medical oncology, M.D. Anderson Cancer Center.

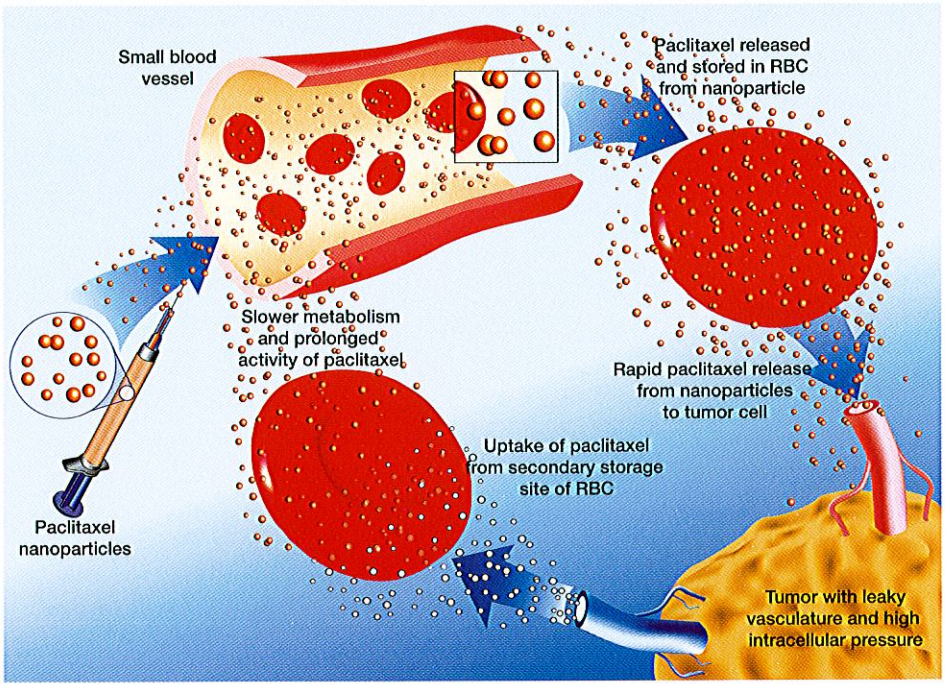
"We have completely done away with the cremophor formulation, which translates into lack of hypersensitivity reactions," said Michael J. Hawkins, MD, chief medical officer of American BioScience, Inc., Santa Monica, California, which is developing the agent. "None of the patients required any premedication whatsoever—they just receive the drug as a straight 30-minute infusion."

Because paclitaxel has a poor aqueous solubility, cremophor is used to make a soluble formulation of the drug. Entrapment of paclitaxel within cremophor micelles in the plasma compartment may result in suboptimal paclitaxel intracellular partitioning, rapid metabolism of paclitaxel, and poor drug availability in tumor tissue. Cremophor-containing paclitaxel has been associated with serious side effects, including serious hypersensitivity reactions.

According to the poster, the albumin-paclitaxel nanoparticles in ABI-007 enhance intratumoral penetration of paclitaxel (see drawing below), with potentially lower toxicity and higher efficacy than the standard formulation.

The poster included data from two multicenter trials, one of which evaluated ABI-007 at its maximum tolerated dose of 300 mg/m^2 via a 30-minute IV infusion every 3 weeks; 37 patients par-

Paclitaxel Nanoparticles Penetrate Tumor



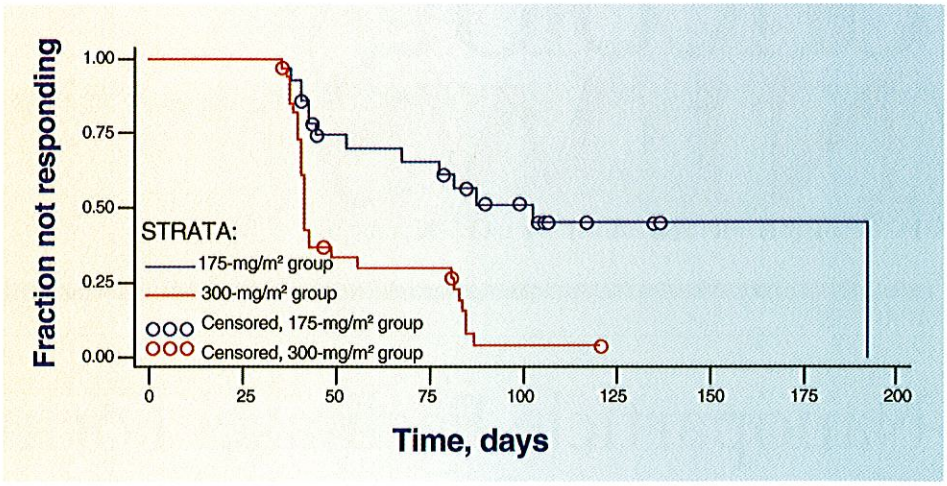
ABI-007 is a protein-engineered, biologic nanotransporter designed to enhance the cellular penetration of paclitaxel. The albumin-based nanoparticles cause rapid release of paclitaxel to cells and tissue, with storage of the active molecule in circulating red blood cells, increased drug delivery to the tumor, and sustained activity with prolonged half-life of the parent molecule. Reproduced with permission of American Pharmaceutical Partners, Inc.

ticipated. The other trial included 30 patients treated with 175 mg/m² infusions. The patients had received no prior chemotherapy or adjuvant therapy only. No steroid premedication or growth factor support was used in either trial. Of the 67 patients, 62 were evaluable for response, including 34 in the 300 mg/m² trial and 28 in the 175 mg/m² trial.

Dose-Response Effect

The investigators observed a significant dose-response effect, with an overall response rate (complete plus partial response) of 86% in the 300 mg/m² group vs 50% in the lower-dose group (P = .002). In addition, time to first response was significantly shorter in the higher-dose group: 1.4 months vs 3.4 months (P < .001) (see Figure above).

The nanoparticle paclitaxel formulation was well tolerated in both groups, investigators said. Myelosuppression was the most common toxicity, with grade 4 neutropenia occurring in 16% of patients (24% and 7% of patients in the 300 and 175 mg/m² dose groups, respectively).



There was one case of neutropenic fever (3%) in the 300 mg/m² group. Neuropathy of grade 3 or greater occurred in five patients (14%) in the higher-dose group. There were no serious (grade 3-4) hypersensitivity reactions.

Phase III Trial

A multicenter, randomized, phase III trial directly comparing ABI-007 and standard-formulation paclitaxel in metastatic breast cancer has been completed. That 460-patient trial compared paclitaxel and ABI-007 on antitumor activity and toxicity, including not only hypersensitivity reactions but also other paclitaxel-associated adverse effects such as neurotoxicity. "It may be that the cremophor is also contributing to the Taxol toxicity as a separate issue from the hypersensitivity reactions," Dr. Hawkins said." ONI

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Nanoparticle Paclitaxel Doubles Response Rate

■ SAN ANTONIO—Homogenizing paclitaxel with human serum albumin under pressure produces nanoparticles that become a colloid when mixed with ordinary saline, are less toxic than standard Taxol, and are much more effective at delivering paclitaxel into the tumor, researchers said at the 26th Annual San Antonio Breast Cancer Symposium (abstract 44). [A preliminary report of this study appeared in ONI November 2003, page 2.]

Joyce O'Shaughnessy, MD, reported a phase III trial in metastatic breast cancer that showed the new formulation, known as ABI-007 (Abraxane), produced higher overall response rates, longer time to progression, and significantly less hematologic toxicity than Taxol without the use of prophylactic steroids. "This formulation permits a shorter infusion schedule, gives a higher response rate, and causes less neutropenia than Taxol," said Dr. O'Shaughnessy, co-director, Breast Cancer Research, U.S. Oncology.

This trial is expected to provide pivotal data for the FDA's review of ABI-007, which was given fast-track status earlier this year. It was sponsored by American Pharmaceutical Partners, Inc., a subsidiary of American BioScience, Inc., where the drug was developed.

ABI-007 was created as a way of transporting paclitaxel, which is highly insoluble in aqueous solutions, into the tumor cell. Taxol accomplishes this by using the castor oil derivative Cremophor as a carrier, but researchers have long suspected that Cremophor contributes to hypersensitivity reactions as well as to the hematologic and neurologic toxicities associated with Taxol. Cremophor also leaches

Dr. O'Shaughessy

plasticizers out of conventional polyvinylchloride (PVC) tubing; as a result, Taxol must be mixed in glass bottles or in non-PVC infusion systems with in-line filtration. ABI-007 can be reconstituted in normal saline and does not require any special handling.

Not only does albumin not cause these Cremophor-associated problems but it is actively transported across cell membranes by a nonsaturable mechanism.

Higher response rate vs Taxol in metastatic breast cancer

Patients in the phase III trial were randomized to ABI-007 260 mg/m² given over 30 minutes IV without routine premedication (n = 229) every 3 weeks or to Taxol 175 mg/m² given over 3 hours IV with dexamethasone and antihistamine premedications (n = 225) every 3 weeks. The difference in infusion times reflects the fact that ABI-007 can be reconstituted in normal saline at a paclitaxel concentration of 2 to 10 mg/mL vs 0.3 to 1.2 mg/mL for Taxol, which requires correspondingly greater volumes and longer infusion times.

All patients had metastatic disease and no prior taxanes; 40% had liver-dominant disease; one third had lung-dominant disease; three fourths had prior treatment with anthracyclines, half of which had been for metastatic disease.

The primary endpoint was confirmed overall response rate (complete response plus partial response) of target lesions after six cycles of treatment. Response was judged by RECIST (Response Evaluation Criteria in Solid Tumors) and had to be documented by cycle 4 to permit confirmation by cycle 6. Responses were verified by a blinded independent radiology team. Secondary endpoints were time to progression and overall survival, but Dr. O'Shaughnessy said that median survival has not yet been reached.

Study Results

The median number of cycles delivered in the trial was six for ABI-007 and five for Taxol, with median delivered doses of 255 mg and 171 mg, respectively. The mean total paclitaxel doses delivered were 1,459 mg/m² with ABI-007 and 909 mg/m² with Taxol. "The mean delivered dose of paclitaxel was 60% higher with ABI-007," Dr. O'Shaughnessy said.

ABI-007 produced significantly more overall responses than Taxol (21% vs 10%, P = .002, on independent radiology review response assessment). Time to tumor progression was also significantly longer (21.9 weeks vs 16.1

weeks, P = .029). The higher response rate with ABI-007 was noted both for first-line patients and for those who had prior chemotherapy for metastatic disease, as well as for patients with poor prognostic indicators such as liver or lung metastases.

Toxicity

Grade 3 neutropenia was 25% with ABI-007 vs 31% with Taxol, and grade 4 neutropenia was 9% vs 22% (P < .009). Median ANC nadir was 1,350 vs 900/mm³ (P < .001). However, the clinical importance of this difference is not clear, since the neutropenia was not associated with increased risk of febrile neutropenia (which occurred in less than 1% of patients in each group) or of infection, and there were no septic deaths. Thrombocytopenia occurred in less than 1% of patients in each group.

There was significantly more grade 3 sensory neuropathy with ABI-007 (10% vs 2%, P < .001). There were no episodes of grade 4 neuropathy. Dr. O'Shaugh-nessy said that the grade 3 neuropathies associated with ABI-007 improved to grade 1-2 in a median of 22 days. The researchers suspect that the increased neurotoxicity seen in the ABI-007 arm was due to the higher dose of paclitaxel actually delivered.

There were no grade 3-4 hypersensitivity reactions following ABI-007 despite the absence of premedication.

Mechanism of Rapid Transport

Dr. O'Shaughnessy said that work reported separately by Neil Desai, PhD, of American Bioscience, Inc., Santa Monica, California, showed that an albumin-specific receptor (gp60 or albondin) rapidly binds and transports albumin across endothelial cells of the tumor microvasculature into the tumor tissue space. She suggested that this mechanism might be responsible for the more rapid transport of paclitaxel into the tumor with ABI-007 and that, in contrast, Cremophor actually inhibits the binding of paclitaxel to tumor vessel endothelial cells.

In a poster presentation (abstract 524), Dr. Desai and his colleagues said that in addition to carrying paclitaxel, Cremophor also forms micelles within which the drug becomes entrapped. This may account for the observed lack of dose response relationship with Taxol in breast cancer. Cremophor itself has also been shown to interfere with paclitaxel efficacy by arresting cells in the G1 phase of the cell cycle, thus preventing target cells from entering the mitosis phase in which paclitaxel is most effective (*Investigational New Dru 19:125-141, 2001*).

"ABI-007 permits paclitaxel dosing of 260 mg/m² over 30 minutes without requirement for steroids or other premedication, and it produces higher objective response rates, longer time to progression, and fewer side effects than Taxol," she said. "Weekly ABI-007 produced virtually no toxicity in previously taxane-refractory patients, and a weekly trial of front-line ABI-007 is being planned."

I. Craig Henderson, MD, of the University of California, San Francisco, who participated in a press conference discussing the study, called for a head-to-head trial comparing ABI-007 to docetax-el (Taxotere) in metastatic breast cancer. Dr. Henderson also raised a concern about whether clinicians might quickly shift from Taxol to ABI-007 if the drug is approved by the FDA. "I would need to see phase II data on ABI-007 in previously untreated patients before I would say it should be substituted for weekly Taxol," Dr O'Shaughnessy said. ONI

In January 2005, the U.S. Food and Drug Administration (FDA) app

In January 2005, the U.S. Food and Drug Administration (FDA) approved the use of the drug, Abraxane to help treat women with advanced, metastatic breast cancer —the type of cancer that has spread past the breast and lymph nodes to other areas of the body. The drug can be used in women who have been unsuccessfully treatment with combination chemotherapy or who have relapsed within 6 months of chemotherapy. Abraxane is a new form of the drug, Taxol (generic name, paclitaxel) that may have fewer side effects.

In a clinical trial comparing Abraxane and Taxol, 460 eligible women with advanced breast were given either drug. Those who received Abraxane saw their tumors shrink by 21.5% compared with 11.1% among the women who received Taxol.

"Abraxane provides a much-needed new treatment option for women with metastatic breast cancer," said lead clinical trial investigator William J. Gradishar, MD, Associate Professor of Medicine at the Lynn Sage Breast Cancer Program, Northwestern Memorial Hospital, in an American Pharmaceutical Partners news release. "The pivotal clinical trial results demonstrated that Abraxane had superior response rate when compared to Taxol in patients with metastatic breast cancer."

Taxol has been approved by the FDA for several years to treat breast cancer. However, it must be dissolved in a toxic solvent before administration, which causes allergic reactions in some patients. To counteract these reactions, steroids and antihistamines are given to patients before treatment.

According to American Pharmaceutical Partners, Inc., the marketer of Abraxane, its drug contains no toxic substances and does not require any premedication, as with Taxol. Abraxane belongs to a new class of drugs of "protein-bound particle" drugs. Patients who receive Abraxane can receive larger doses of the drug before it becomes intolerable.

In the clinical trial, slightly fewer women who took Abraxane experienced neutropenia—a condition marked by a sharp decrease in white blood cells—compared to those who took Taxol (82% to 80% respectively). Neutropenia can increase the risk of infection. However, patients on both drugs are warned that neutropenia is a possible side effect.

Other side effects noted in the clinical trial for both Abraxane and Taxol included anemia, infections, swelling, nausea, vomiting and diarrhea. Patients on Abraxane experienced more cases of nerve damage, severe pain in the muscles or joints, and vomiting than patients on Taxol.

"It's important that the entire breast cancer community constantly challenge the status quo and push each other to provide a better treatment for those with the disease," said Marisa Weiss, MD, oncologist, an American Pharmaceutical Partners news release. "This advance represents an exciting new treatment option for women with metastatic breast cancer."

The January 7, 2005 American Pharmaceutical Partners news release, FDA Approves Abraxane, First In New Class Of Protein-Bound Particle Drug For Metastatic Breast Cancer, was accessed at http://www.appdrugs.com/

Full prescribing information for Abraxane is available at http://www.abraxane.com/

To learn more about Taxol, please visit http://www.imaginis.com/breasthealth/bc_drugs.asp#Taxol